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54 **Tetrahydrocarbazole 1-alkanoic acids.**

57 Tetrahydrocarbazole 1-alkanoic acids are disclosed. The compounds act as prostaglandin and thromboxane antagonists and are useful in treating asthma, diarrhea, hypertension, angina, platelet aggregation, cerebral spasm, premature labor, spontaneous abortion and dysmenorrhea and as cytoprotective agents.

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TITLE OF THE INVENTION

TETRAHYDROCARBAZOLE 1-ALKANOIC ACIDS

BACKGROUND OF THE INVENTION

5 This invention relates to prostaglandin antagonists useful in treating a variety of conditions, such as allergic asthma where excessive contractile activity of prostaglandins and prostaglandin biosynthetic intermediates occur.

10 These compounds antagonize the actions of contractile prostaglandins, such as $\text{PGF}_{2\alpha}$, PGG_2 , PGH_2 , PGD_2 and TXA_2 . The use of agents which act as prostaglandin antagonists offers new approaches to therapy in a number of disease states.

15 For example, certain prostaglandins, such as $\text{PGF}_{2\alpha}$, PGD_2 , PGG_2 , and PGH_2 , are potent bronchospastic agents. Indeed human asthmatics have been shown to be especially sensitive to the bronchial constricting action of $\text{PGF}_{2\alpha}$.

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The compounds of the present invention are also antithrombotic agents. Thus, they are useful in the treatment and/or prevention of thromboembolic diseases such as arterial thrombosis and those
5 involving platelet deposition, e.g. prothesis.

In addition to the involvement of contractile prostaglandins in asthma, prostaglandins are known to play a role in other allergic conditions, as well as, diarrhea, hypertension,
10 angina, platelet aggregation, cerebral spasm, cerebral ischemia, arrhythmia, circulatory shock, sudden death, atherosclerosis, myocardial ischemia, premature labor, spontaneous abortion, dysmenorrhea, glomerular nephritis, and systemic lupus erythem-
15 atosis. Consequently, the compounds of this invention will alleviate the above mentioned diseases.

In addition to the prostaglandin antagonist actions, the compounds of this invention are inhibitors of the biosynthesis of 5-lipoxygenase
20 metabolites of arachidonic acid, such as 5-HPETE, 5-HETE and the leukotrienes. Leukotrienes B₄, C₄, D₄ and E₄ are known to contribute to various disease conditions such as asthma, psoriasis, pain, ulcers and systemic anaphylaxis. Thus
25 inhibition of the synthesis of such compounds will alleviate these and other leukotriene-related disease states.

The compounds of the present invention may be used to treat or prevent mammalian (especially,
30 human) disease states such as erosive gastritis; erosive esophagitis; ethanol-induced hemorrhagic erosions; hepatic ischemia; noxious agent induced

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damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic
5 damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure.

Certain 9-benzyl-1,2,3,4-tetrahydro-carbazole acetic acids or esters thereof are shown as
10 chemical intermediates in the preparation of carbazoles that are known in the art as anti-inflammatory, analgesic and anti-rheumatic agents (see U.S. Patent 3,896,145 and British Patent 1,385,620). Certain 9-benzyl-1,2,3,4-tetrahydro-
15 carbazole carboxylic acids are known in the art as anti-inflammatory, analgesic and anti-rheumatic agents (see U.S. Patents 3,868,387; 4,009,181; 3,905,998 and 3,758,496), and 9-benzyl-carbazole carboxylic acids (U.S. Patents 3,956,295 and
20 4,057,640) and 9-benzylcarbazole acetic acids and esters thereof (U.S. Patent 3,896,145 and British Patent 1,385,620) are known as anti-inflammatory, analgesic and anti-rheumatic agents. None of these compounds, however, are shown to be prostaglandin, or
25 thromboxane antagonists or inhibitors of leukotrine biosynthesis.

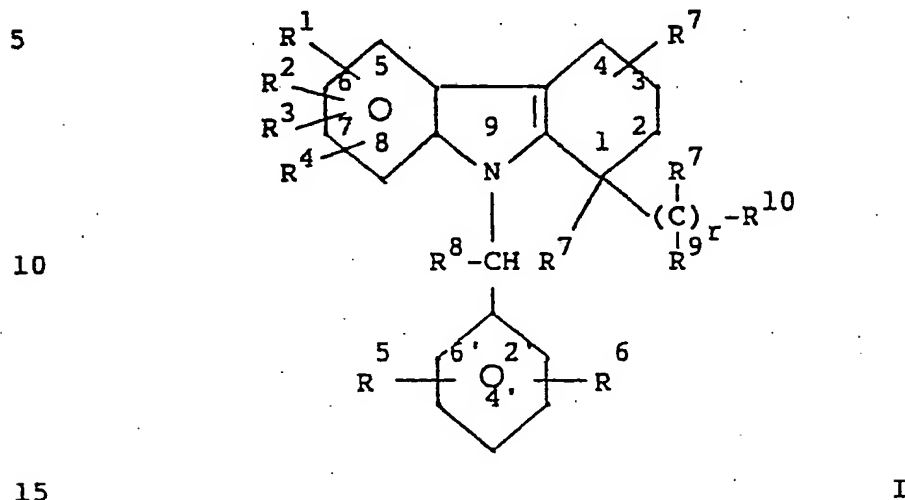
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DESCRIPTION OF THE INVENTION

The present invention relates to novel compounds of Formula I:



wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently selected from:

- 20
- (1) hydrogen;
 - (2) alkyl having 1 to 6 carbon atoms;
 - (3) alkenyl having 2 to 6 carbon atoms;
 - (4) $-(CH_2)_n^M$
- wherein n is 0 to 3 and M is
- 25
- a) OR^{13} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{13} ;
 - e) phenyl or substituted phenyl
- 30
- wherein substituted phenyl is as defined below in the definition of R^{13} ;

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- f) COOR^{14} ;
- g) $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^{15}$;
- h) tetrazole;
- i) $-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^{16}$ wherein R^{16} is C_1 to C_6 alkyl, benzyl or phenyl;
- 10 j) $-\text{NR}^{14}\text{R}^{14}$;
- k) $-\text{NHSO}_2\text{R}^{17}$ wherein R^{17} is C_1 to C_6 alkyl, 4-methylphenyl, phenyl, or CF_3 ;
- 15 l) $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{CH}_2\text{OH}$;
- m) $-\text{SOR}^{13}$;
- n) $-\text{CONR}^{14}\text{R}^{14}$;
- 20 o) $-\text{SO}_2\text{NR}^{14}\text{R}^{14}$;
- p) $-\text{SO}_2\text{R}^{13}$;
- q) NO_2 ;
- r) $-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^{15}$;
- 25 s) $-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NR}^{14}\text{R}^{14}$;
- t) $-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{OR}^{16}$;
- v) N_3 ;
- 30 u) CN ;
- R^7 is H or alkyl of 1 to 6 carbons;
- R^8 is H or alkyl of 1 to 6 carbon atoms;

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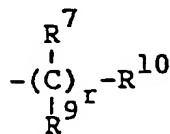
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- each R^9 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons;
 R^{10} is COOH; CH_2OH ; CHO; tetrazole;
 $NHSO_2R^{11}$ wherein R^{11} is OH, alkyl or alkoxy of
 5 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl
 or phenyl substituted by alkyl or alkoxy groups of 1
 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or
 acyl to 1 to 6 carbons; $CONHSO_2R^{11}$; hydroxy-
 methylketone; CN; or $CON(R^9)_2$;
 10 r is 1 to 6;
 each R^{13} independently is H; C_1 to C_6
 alkyl; benzyl; phenyl or substituted phenyl wherein
 the substituents are C_1 to C_3 alkyl, halogen, CN,
 CF_3 , $COOR^{14}$, CH_2COOR^{14} , C_1 to C_3 alkoxy,
 15 or C_1 to C_4 perfluoroalkyl;
 each R^{14} is independently H, phenyl,
 benzyl or C_1 to C_6 alkyl; and,
 each R^{15} independently is H,
 $(CH_2)_mCOOR^{14}$ wherein m is 0 to 4, C_1 to C_6
 20 alkyl, CF_3 , phenyl, or substituted phenyl wherein
 substituted phenyl is as defined above in the
 definition of R^{13} ;
 or a pharmaceutically acceptable salt thereof.

As used herein, the terms "each
 25 independently" or the equivalents thereof are employed
 to describe a number of possible position isomers
 and/or structural variations. For example, as
 described above, the following unit is attached to
 position 1 of the tetrahydrocarbazole ring:

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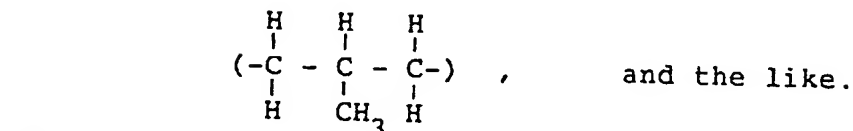
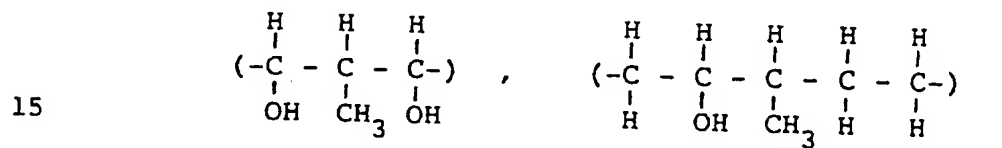
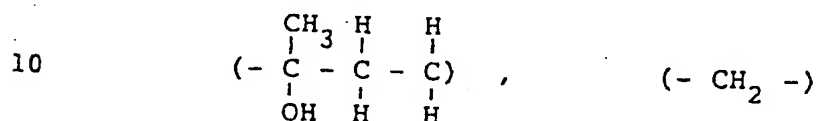


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The letter r represents possible alkane chains of from 1 to 6 carbon atoms, each having the R^7 and R^9 substituent groups. On each carbon atom of the alkane chain, the R^7 and/or R^9 substituent may be different. The above description therefore contemplates structures such as the following for the segment $-(CR^7R^9)_r-$:



If an R^9 is OH and R^{10} is CO_2H , such compounds may form a lactone, and such lactones are to be regarded as part of the present invention.

The alkyl groups referred to above may be straight chain or branched or may include cycloalkyl groups. As used herein, the term "lower" as applied to alkyl, acyl, alkoxy and the like, unless stated otherwise refers to groups having 1 to 6 carbon atoms. Halogen or halo means fluoro, chloro, bromo and/or iodo.

Pharmaceutically acceptable salts of the compounds described herein are included within the

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scope of the present invention. Such salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, 5 potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the potassium, sodium calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic 10 non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, tri-methylamine, diethanolamine, diethylamine, 15 triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylamino-ethanol, tomethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, imidazole, betaine, ethylenediamine, glucosamine, methylglucamine, 20 theobromine, purines piperazine, N,N-dibenzyl-ethylenediamine, piperidine, N-ethyl-piperidine, morpholine, N-ethylmorpholine, polyamine resins and the like.

Preferred compounds of the present invention 25 comprise the compounds of formula I wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently selected from:

- (1) hydrogen;
- 30 (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4) $-(CH_2)_n^M$

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wherein n is 0 or 1 and M is as defined previously for Formula I;

R^{10} is COOH; CH_2OH ; CHO; tetrazole;
 5 $CONHSO_2R^{11}$ wherein R^{11} is OH, alkyl or alkoxy
 of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,
 phenyl or phenyl substituted by alkyl or alkoxy
 groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN,
 formyl or acyl to 1 to 6 carbons; hydroxymethylketone;
 CN; or $CON(R^9)_2$;

10 r is 1 to 6; and the remaining substituents
 are as defined previously for Formula I.

More preferred compounds of the present
 invention comprise the compounds of Formula I.
 wherein:

15 R^1, R^2, R^3, R^4, R^5 and R^6 are
 each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- 20 (4) M wherein M is as defined initially for
 Formula I;

R^{10} is COOH; CH_2OH ; CHO; tetrazole;
 hydroxymethylketone;

r is 1 or 2; and the remaining substituents
 25 are as defined initially for Formula I.

Most preferred compounds of the present
 invention comprise the compounds of Formula I.
 wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are
 30 each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;

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(3) M wherein M is

- a) OR^{13} ;
- b) halogen;
- c) CF_3 ;
- 5 d) SR^{13} ;
- e) COOR^{14} ;
- f) $-\overset{\text{O}}{\parallel}\text{C}-\text{R}^{15}$;
- 10 g) tetrazole;
- h) $-\text{SOR}^{13}$;
- i) $-\text{CONR}^{14}\text{R}^{14}$;
- j) $-\text{SO}_2\text{NR}^{14}\text{R}^{14}$;
- k) $-\text{SO}_2\text{R}^{13}$;
- 15 l) $-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{R}^{15}$;
- m) CN;
- n) N_3 ;

each R^9 is independently H, or alkyl of 1 to 4 carbons;

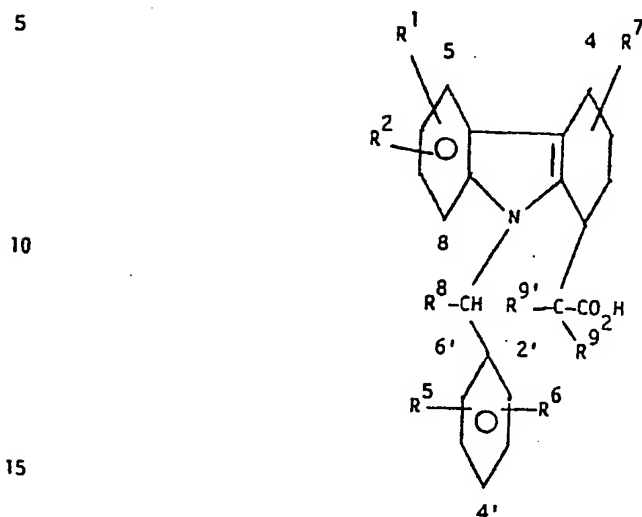
20 R^{10} is COOH; or tetrazole;

r is 1 and the remaining substituents are as defined initially for Formula I.

In the above most preferred embodiment, those compounds are particularly preferred wherein at
 25 least one of R^1 to R^4 is not hydrogen; one of R^5 or R^6 is not hydrogen; R^7 is hydrogen; R^9 is hydrogen, and the remaining substituents are as defined in the most preferred embodiment.

A further embodiment of the present
 30 invention are the following novel compounds (Table 1). Among the resolved isomers in Table 1, the (-) isomers, compounds 3, 37, 39 and 41, are preferred.

Table 1
Novel Tetrahydrocarbazole
Alkanoic Acids



Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
20 1 (Ex. 1)	6-F	H	4'-Cl	H	H, H	H	H
2 (Ex. 4)	6-OMe	H	4'-Cl	H	H, H	H	H
25 3 (Ex. 7)	6-F	H	4'-Cl	H	H, H	H	H
	(-) isomer						
4 (Ex. 8)	6-F	H	4'-Cl	H	H, H	H	H
	(+) isomer						
30 5 (Ex. 9)	6-F	H	H	H	H, H	H	H
6 (Ex. 10)	6-F	H	4'-OMe	H	H, H	H	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	7 (Ex. 11)	6-F	H	3'-Cl	4'-Cl	H, H	H	H
5	8 (Ex. 12)	6-F	H	H	H	H, H	H	Me
	9 (Ex. 13)	H	H	4'-Cl	H	H, H	H	H
	10 (Ex. 14)	6-Cl	H	4'-Cl	H	H, H	H	H
10	11 (Ex. 15)	8-Me	H	4'-Cl	H	H, H	H	H
	12 (Ex. 16)	6-Br	H	4'-Cl	H	H, H	H	H
15	13 (Ex. 17)	6-Me	H	4'-Cl	H	H, H	H	H
	14 (Ex. 19)	8-F	H	4'-Cl	H	H, H	H	H
	15 (Ex. 20)	6-F	H	4'-Cl	H	H, H	3-t-Bu	H
20	16 (Ex. 21)	5-F	H	4'-Cl	H	H, H	H	H
	17 (Ex. 21)	7-F	H	4'-Cl	H	H, H	H	H
25	18 (Ex. 22)	5-Cl	7-Cl	4'-Cl	H	H, H	H	H
	19 (Ex. 23)	6-Cl	8-Cl	4'-Cl	H	H, H	H	H
	20 (Ex. 18)	6-F	H	4'-Cl	H	Me, H	H	H
30	21	6-F	H	4'-Cl	H	Me, Me	H	H
	22	6-F	H	4'-Cl	H	H, H	1-Me	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	23	8-Br	H	4'-Cl	H	H, H	H	H
5	24 (Ex. 24)	6-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
	25 (Ex. 25)	6-C(Me) ₃	H	4'-Cl	H	H, H	H	H
10	26 (Ex. 26)	6-CF ₃	H	4'-Cl	H	H, H	H	H
	27 (Ex. 27)	6-SMe	H	4'-Cl	H	H, H	H	H
	28 (Ex. 28)	6-S(O)Me	H	4'-Cl	H	H, H	H	H
15	29 (Ex. 29)	6-S(O) ₂ Me	H	4'-Cl	H	H, H	H	H
	30 (Ex. 30)	8-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
20	31 (Ex. 31)	8-SMe	H	4'-Cl	H	H, H	H	H
	32 (Ex. 32)	8-S(O)Me	H	4'-Cl	H	H, H	H	H
	33 (Ex. 33)	6-F	H	4'-Cl	H	H, H	3-Me	H
25	34 (Ex. 34)	6-F	8-F	4'-Cl	H	H, H	H	H
	35 (Ex. 35)	6-Me	8-Me	4'-Cl	H	H, H	H	H
30	36 (Ex. 36)	6-OMe	8-Me	4'-Cl	H	H, H	H	H
	37 (Ex. 37)	6-F(-) Isomer	8-F	4'-Cl	H	H, H	H	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	38 (Ex. 38)	6-F(+) Isomer	8-F	4'-Cl	H	H, H	H	H
5	39 (Ex. 39)	8-Me(-) Isomer	H	4'-Cl	H	H, H	H	H
	40 (Ex. 40)	8-Me(+) Isomer	H	4'-Cl	H	H, H	H	H
	41 (Ex. 41)	8-F(-) Isomer	H	4'-Cl	H	H, H	H	H
10	42 (Ex. 42)	8-F(+) Isomer	H	4'-Cl	H	H, H	H	H
	43	6-F	8-F	3'-Cl	4'-Cl	H, H	H	H
15	44	6-F	8-F	2'-Cl	4'-Cl	H, H	H	H
	45	6-F	8-F	4'-OMe	H	H, H	H	H
	46	6-F	8-F	4'-OH	H	H, H	H	H
20	47	6-F	8-F	4'-SMe	H	H, H	H	H
	48	6-F	H	4'-S(O)Me	H	H, H	H	H
25	49	6-F	8-F	4'-NHCOMe	H	H, H	H	H
	50	6-F	H	4'-S(O) ₂ Me	H	H, H	H	H
	51	6-F	H	4'-F	H	H, H	H	H
30	52	6-F	H	4'-Br	H	H, H	H	H

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Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
53	6-F	8-Me	4'-Cl	H	H, H	H	H
5	54	6-F	H	4'-CO ₂ H	H	H, H	H
	55	6-F	H	4'-CO ₂ Me	H	H, H	H
10	56	6-F	8-F	4'-n-C ₃ H ₇	H	H, H	H
	57	6-F	8-F	3'-I	4'-OH	H, H	H
	58	6-F	8-F	4'-I	H	H, H	H
15	59	6-N ₃	H	4'-Cl	H	H, H	H
	60	6-F	H	4'-N ₃	H	H, H	H

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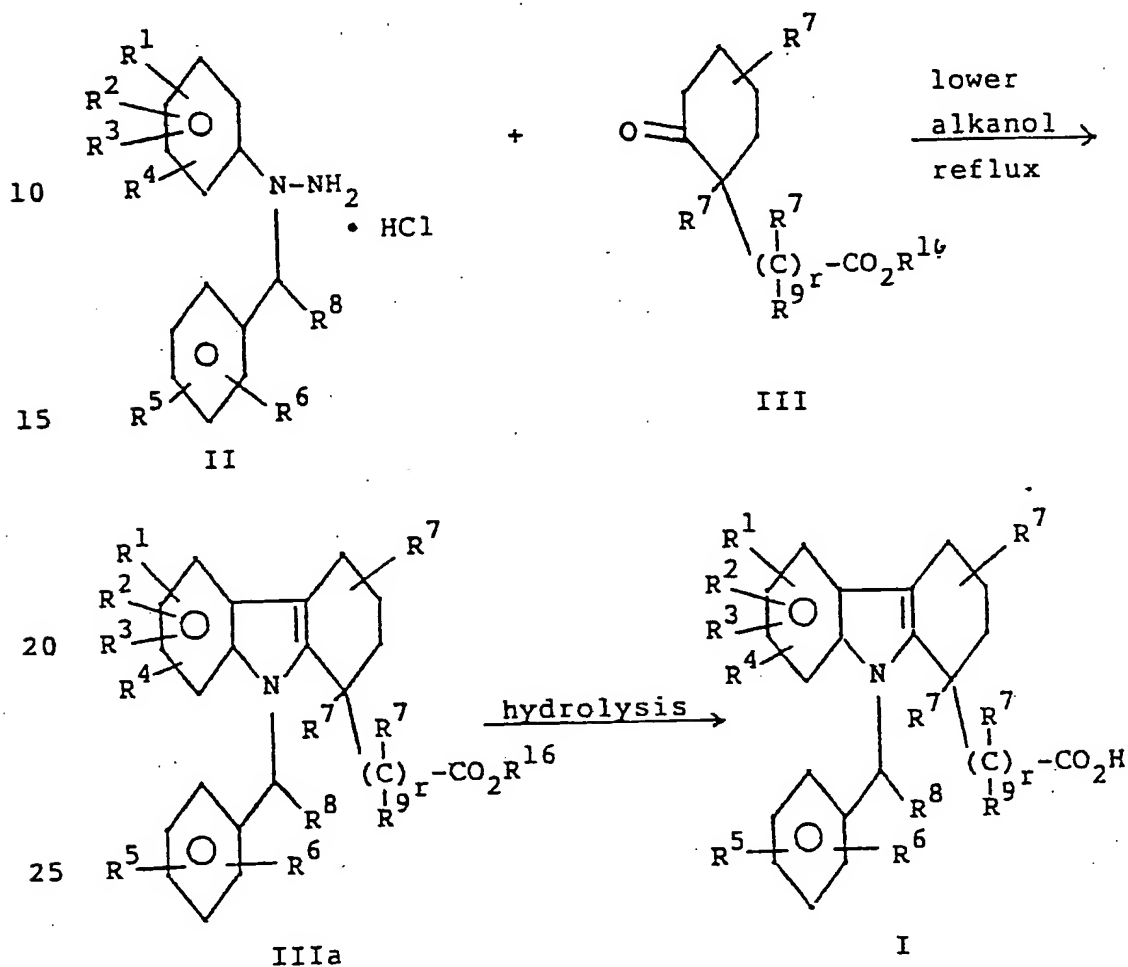
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The following reaction schemes illustrate the preparation of the compounds of the present invention:

5 Scheme IPreparation of Formula I Compounds

The reaction can be conveniently carried out in an alcohol solvent such as t-butanol, i-butanol, and the like. The hydrolysis of the ester intermediates IIIa is conveniently carried out by using

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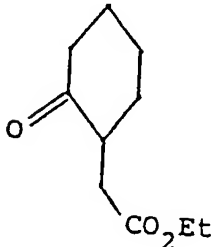
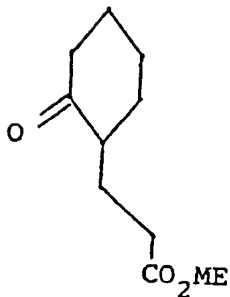
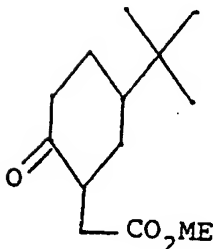
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NaOH or KOH in aqueous ethanol or methanol followed by acidification to obtain compounds of Formula I;

The following ketones (1,2,4) of structure III are known in the art, and ketone 3 is readily prepared by procedures analogous to those for the known ketones.

TABLE 2
ketones of Formula III

No.	Structure	Reference
1.		Ethyl 2-cyclohexanoneacetate; commercially available (Aldrich)
2.		Methyl 2-cyclohexanonepropionate; J.A.C.S. <u>85</u> 207 (1963) G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz and R. Terrell
3.		Methyl 4-tert-butyl-2-cyclohexanoneacetate

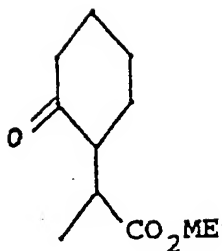
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TABLE 2 (Cont'd)

4.

Methyl 2-(2-cyclohexanone)
propionateJ.A.C.S. 85 207 (1963)

G. Stork, A. Brizzolara,

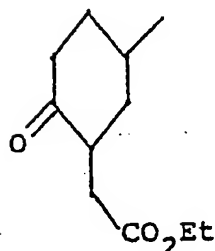
H. Landesman,

J. Smuszkowicz and

R. Terrell

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5.

Ethyl 4-methyl-2-cyclo-
hexanone acetate

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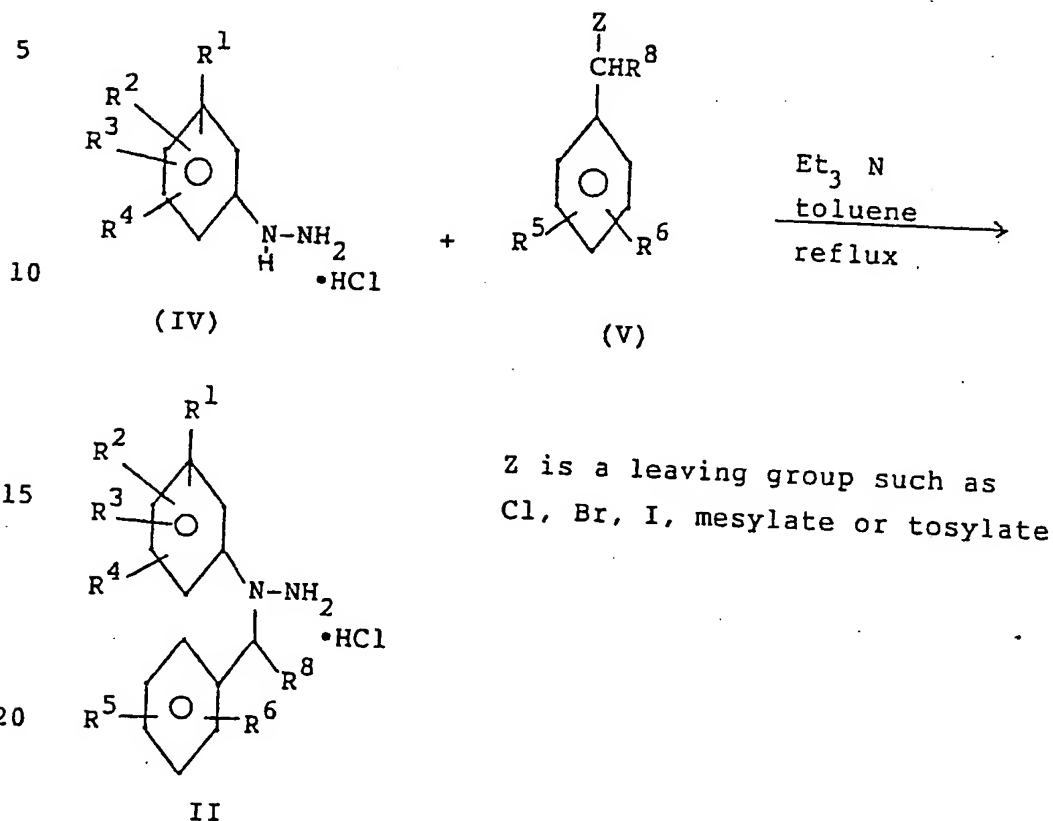
The sequence described above is an applic-
ation of the Fischer Indole Synthesis. Numerous-
indole syntheses are described in reviews, such as,
for example "Heterocyclic Compounds" Volume 25, Parts
I, II, III, W. J. Houlihan (Ed.), Interscience, J.
Wiley & Sons, N. Y., 1979. Appropriate manipulations
of functional groups using sequences described in such
reviews will lead to the compounds of the present
invention.

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Scheme IIPreparation of Hydrazine Derivatives (II)

25 With regard to Scheme II, the preparation of hydrazine starting materials is illustrated by the preparation of 1-(4-chlorobenzyl)-1-(4-methoxyphenyl)-hydrazine. A mixture of 10 g of p-methoxyphenyl-hydrazine hydrochloride, 75 ml of toluene and 11.5 ml of triethylamine was heated at reflux for 60 minutes.

30 Then, 7.1 g of p-chlorobenzyl chloride was added. After stirring 16 hours at reflux, triethylamine hydrochloride was filtered off and washed with ethyl

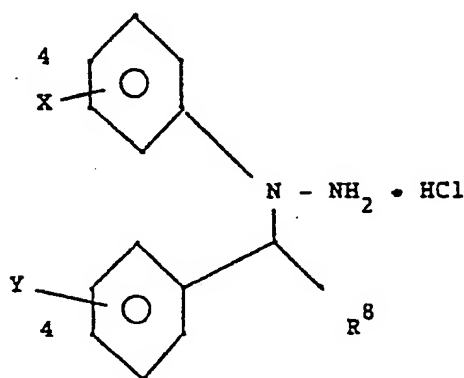
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ether. The filtrate and washing were concentrated in vacuo and chromatographed on a silica gel column (hexane-ethyl acetate, 9:1) to give 6.64 g of 1-(4-chlorobenzyl)-1-(4-methoxyphenyl)hydrazine. Other hydrazines, similarly prepared, are also shown in Table 3, below.

TABLE 3

Hydrazines

Compound				
No.	X	Y	R ⁸	Compound Name
1.	4-F	4-Cl	H	1-(4-chlorobenzyl)-1-(4-fluorophenyl) hydrazine hydrochloride
2.	3,5-Cl ₂	4-Cl	H	1-(4-chlorobenzyl)-1-(3,5-dichlorophenyl)hydrazine hydrochloride

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TABLE 3 (Cont'd)

5	3.	4-OMe	4-Cl	H	1-(4-chlorobenzyl)-1-(4-methoxyphenyl) hydrazine hydrochloride
10	4.	2-Me	4-Cl	H	1-(4-chlorobenzyl)-1-(2-methylphenyl) hydrazine hydrochloride
15	5.	4-Me	4-Cl	H	1-(4-chlorobenzyl)-1-(4-methylphenyl) hydrazine hydrochloride
20	6.	4-Cl	4-Cl	H	1-(4-chlorobenzyl)-1-(4-chlorophenyl) hydrazine hydrochloride
25	7.	H	4-Cl	H	1-(4-chlorobenzyl)-1-(phenyl) hydrazine hydrochloride
30	8.	4-Br	4-Cl	H	1-(4-chlorobenzyl)-1-(4-bromophenyl) hydrazine hydrochloride
	9.	3-F	4-Cl	H	1-(4-chlorobenzyl)-1-(3-fluorophenyl) hydrazine hydrochloride
	10.	2,4-Cl ₂	4-Cl	H	1-(4-chlorobenzyl)-1-(2,4-dichlorophenyl) hydrazine hydrochloride

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TABLE 3 (Cont'd)

	11.	4-F	H	H	1-(benzyl)-1-(4-fluorophenyl) hydrazine hydrochloride
5	12.	4-F	4-OMe	H	1-(4-methoxybenzyl)-1-(4- fluorophenyl) hydrazine hydrochloride
10	13.	4-F	3,4-Cl ₂	H	1-(3,4-dichlorobenzyl)-1- (4-fluoro-phenyl) hydrazine hydrochloride.
15	14.	4-F	H	CH ₃	1-[1-(phenyl)ethyl]-1-(4- fluorophenyl) hydrazine hydrochloride
20	15.	2-F	4-Cl	H	1-(4-chlorobenzyl)-1-(2- fluorophenyl) hydrazine hydrochloride.
	16.	1-[2-(4-chlorophenyl)ethyl]-1-(4-fluorophenyl) hydrazine hydrochloride.			
25	17.	1-(2-propyl)-1-(4-fluorophenyl)hydrazine hydrochloride.			
	18.	4-CH(Me) ₂	4-Cl	H	1-(4-chlorobenzyl)-1-(4-iso- propylphenyl)hydrazine hydrochloride
30	19.	4-C(Me) ₃	4-Cl	H	1-(4-chlorobenzyl)-1-(4-tert- butylphenyl)hydrazine)hydro- chloride

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TABLE 3 (Cont'd)

20.	4-CF ₃	4-Cl	H	1-(4-chlorobenzyl)-1-(4-trifluoromethylphenyl)-hydrazine hydrochloride
5				
21.	4-SMe	4-Cl	H	1-(4-chlorobenzyl)-1-(4-methylthiophenyl)hydrazine hydrochloride
10				
22.	2-CH(Me) ₂	4-Cl	H	1-(4-chlorobenzyl)-1-(2-isopropylphenyl)hydrazine hydrochloride
15				
20				
25				
30				

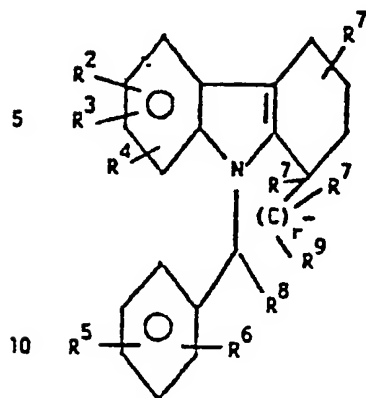
Scheme III illustrates an alternative synthesis of the compounds of Formula I. In this Scheme a Fischer indole synthesis is carried out using a phenylhydrazine IV and the ketone III, followed by hydrolysis. The acid intermediate is then N-benzylated with the reagent V, preferably using a strong base such as potassium t-butoxide to effect the reaction. Acidification of the reaction mixture then yields the free acid of I.

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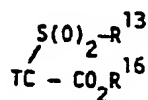
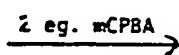
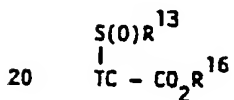
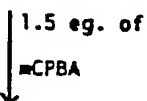
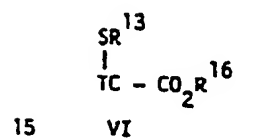
173231A

Scheme IV Preparation of Sulfoxides and Sulfones of Formula I Compounds



= TC below.

 R^1 is replaced by SR^{13} , $S(O)R^{13}$ or

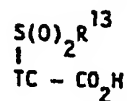
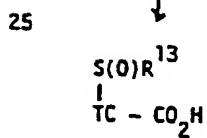
 $S(O)_2R^{13}$
 R^2-R^6 $\neq SR^{13}$ or $S(O)R^{13}$


VIIa

VIIIa

Hydrolysis

Hydrolysis



VII

VIII

30

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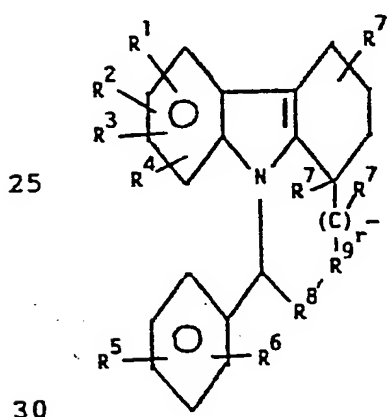
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In Scheme IV is illustrated a method of preparing derivatives of Formula I in which one of the substituents among R^1 - R^4 is a sulfoxide or a sulfone. It will be obvious to one skilled in the art that a sulfoxide or sulfone derivative of R^5 or R^6 could be prepared in the same way.

Ester VI (a representative of III a, Scheme I) is prepared according to Scheme I or Scheme III followed by esterification of acid I. Treatment of VI with a limited amount of an oxidizing agent such as m-chloro-perbenzoic acid yields the sulfoxide ester VIIa, which upon hydrolysis yields sulfoxide acid VII. Further treatment of VIIa with the oxidizing agent, or treatment of VI with an excess (>2 eq.) of the oxidizing agent yields the sulfone ester VIIIa, hydrolysis of which yields the sulfone acid VIII. Both VII and VIII are representatives of Formula I compounds.

20 Scheme V Preparation of Further compounds of Formula I

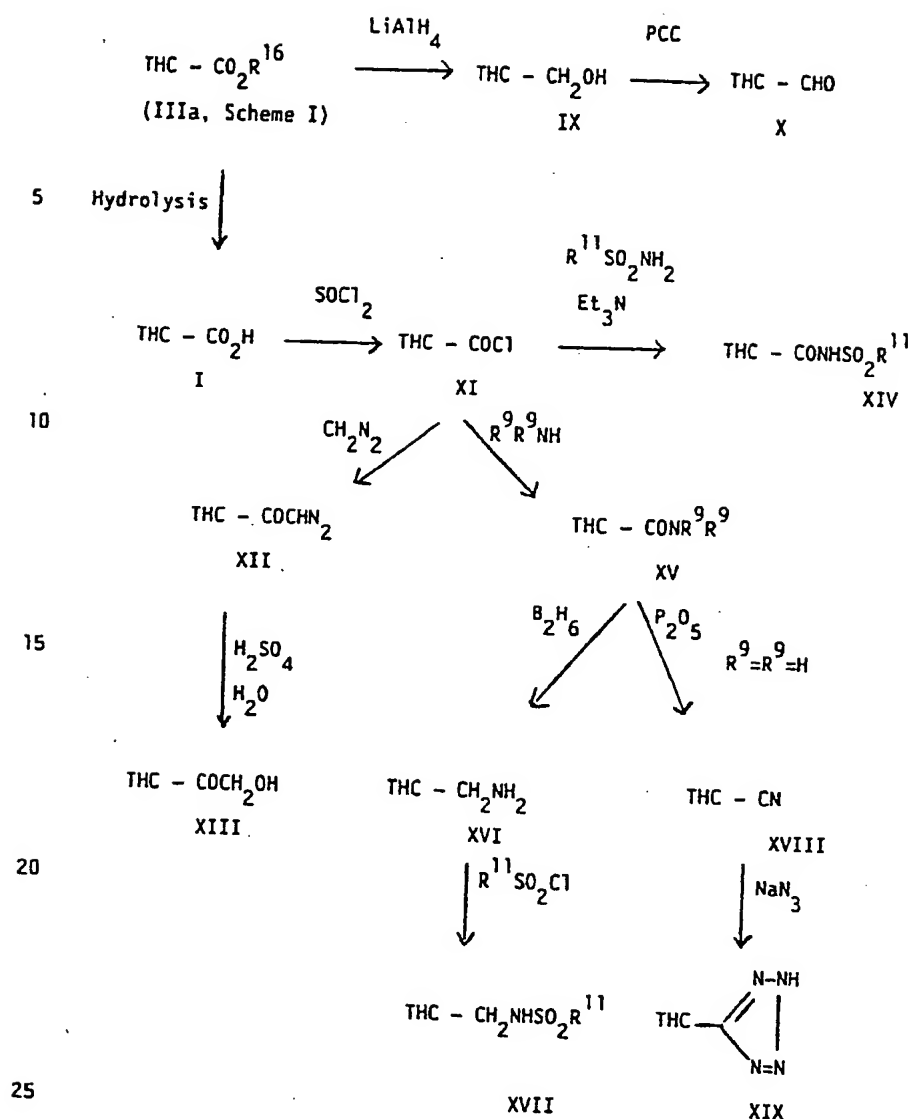


= THC below

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Other compounds of Formula I can be prepared as indicated in Scheme V. Thus the ester derivative IIIa can be reduced to the alcohol IX by lithium aluminum hydride or other suitable reducing agents. Alcohol IX can then be oxidized to aldehyde X by pyridinium chlorochromate or other suitable oxidizing agents. Carboxylic acids of Formula I can be converted to the acid chloride XI (the acid bromide

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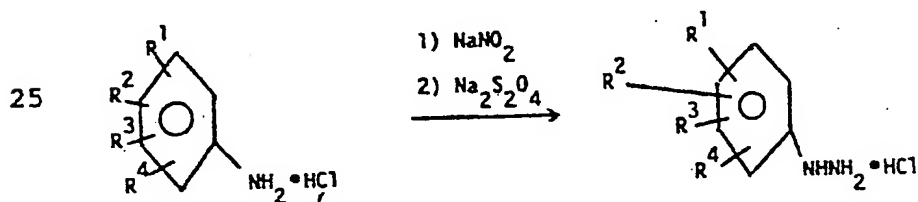
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or a mixed carbonate anhydride could also be used) which when reacted with diazomethane yields the diazoketone XII. Compound XII, upon reaction with aqueous acid, preferably a nonnucleophilic acid such as sulfuric acid or p-toluenesulfonic acid, is converted to the hydroxymethyl ketone XIII.

Acid chloride XI, upon reaction with a sulfonamide, $R^{11}SO_2NH_2$, in the presence of a weak base yields the acyl-sulfonamide XIV. Reaction of XI with an amine, R^9R^9NH , yields amide XV. Amide XV can be sequentially reduced, to amine XVI, with diborane or lithium aluminum hydride, and sulfonylated with $R^{11}SO_2Cl$ to produce sulfonamide XVII. Amide XV (when both R^9 substituents are hydrogen) can be dehydrated by standard reagents to nitrile XVIII, which is converted to tetrazole XIX by reaction with sodium azide, tri-n-butyltin azide or other suitable methods. Compounds IX, X, XIII, XIV, XV, XVII, XVIII and XIX are representatives of Formula I compounds.

Scheme VI Preparation of Hydrazine Derivatives IV



30

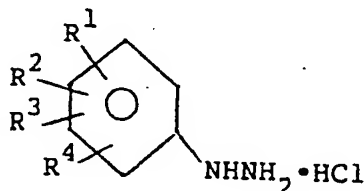
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With regard to Scheme VI, the preparation of hydrazine starting materials is illustrated by preparation of 4-methylthiophenyl hydrazine hydrochloride. 4-Methylthioaniline (13.9 g) was added dropwise to cold HCl (6N) (50 mL) and stirred for 5 min in an ice bath. A solution of NaNO_2 in water (7.25 g, 15 mL) was then added dropwise and stirred for 15 min. The cold diazonium salt was then cannulated into a stirred cold solution of $\text{Na}_2\text{S}_2\text{O}_4$ in water (50 g, 250 mL). After 20 min, ether (200 mL) was added and the reaction mixture basified with NaOH(10N). The ether layer was decanted, washed with brine, dried over Na_2SO_4 and HCl gas was passed through the ether solution to form the hydrochloride salt which precipitated out. After filtration, there was obtained 7.0 g of pure final product. Other hydrazines, similarly prepared, are also shown in Table 3a, below.

TABLE 3a

HYDRAZINES

30

<u>No.</u>	<u>R¹</u>	<u>R²</u>	<u>Compound Name</u>
1	4-SMe	H	4-methylthiophenyl hydrazine hydrochloride

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TABLE 4 (Cont'd)

2	2-CH(Me) ₂	H	2-isopropylphenyl hydrazine hydrochloride
5			
3	2-SMe	H	2-methylthiophenyl hydrazine hydrochloride
4	2-Me	4-Me	2,4-dimethylphenyl hydrazine hydrochloride
10			
5	2-Me	4-OMe	4-methoxy-2-methylphenyl hydrazine hydrochloride
15			
	$R^3 = R^4 = H$		

In those instances when asymmetric centers are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques known to the skilled artisan.

The prostaglandin antagonist properties of the compounds of the present invention can be demonstrated by a number of biological assays, two of which, inhibition of platelet aggregation and measurement of pA_2 values are described below.

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Inhibition of Induced Threshold Aggregation of Human Platelets

Human platelet rich plasma (PRP) is prepared from venous blood of male volunteers who have taken
5 no medication for ten days prior to test. Blood is transferred into plastic centrifuge tubes containing 3.8% Trisodium Citrate in 0.9% NaCl (in a ratio of blood to anticoagulant of 9:1), mixed by gentle inversion, and centrifuged at room temperature for
10 ten minutes at 116 g. The supernatant (PRP) is transferred into plastic tubes. Platelet poor plasma (PPP) is obtained by centrifuging the residual blood cells at 4000 g for ten minutes. PRP is left to stand at least one half hour prior to testing.

15 Platelet Aggregation is measured using a Payton Aggregometer and Recorder. Following calibration of the instrument, a cuvette containing PRP (225 microliters) is incubated for three minutes at 37°C. Drug vehicle (control), or a drug concentra-
20 tion is then added in a volume of 0.5 microliter. After one minute, the aggregating agent (U44069, 9,11-dideoxy-9 α ,11 α -epoxymethano PGF_{2 α}) is added to the cuvette in a volume of 25 microliters. Recording is continued until the maximal response is
25 obtained.

The threshold (approximately 20 - 30% of maximum) aggregation concentration of the agonist to be used is first determined in the presence of the drug vehicle (control). Test compounds are then
30 assayed at 10 or 30 micrograms/ml initially, and if active, are further tested in order to determine the concentration range at which 20-80% of the threshold

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aggregatory response is inhibited. All drugs are dissolved in dimethylsulfoxide.

The height of the aggregation response (measured in divisions of the recorder paper, 1 division = 2.5 mm) in the presence of the drug is recorded, and calculated as percent inhibition of the mean height of the control threshold responses. The IC_{50} (drug concentration which inhibits 50% of the aggregatory response) is obtained by regression analysis.

Estimation of pA_2 Values in Guinea Pig Tracheal Chain

Male albino Hartley strain guinea pigs (300-350 gm) were sacrificed by a blow to the head and exsanguinated. The trachea was removed, freed of extraneous tissue and sectioned into rings of 1-2 mm thickness. Five rings were tied together in series, ensuring that the tracheal muscle lay in the same vertical plane, and the cartilage of each ring then separated at a point directly opposite the muscle. The chains were suspended under 1 gm resting tension in modified Krebs solution (NaCl, 6.87; $NaHCO_3$, 2.1; dextrose, 2.1; KCl, 0.32; $CaCl_2$, 0.28; $MgSO_4 \cdot 7H_2O$, 0.11; KH_2PO_4 , 0.16; gm/L: equilibrated with 5% CO_2 in O_2 for 1 hour) containing indomethacin ($1.4 \times 10^{-5}M$) to suppress endogenous prostaglandin synthesis. Organ bath temperature was maintained at 37°C and 5% CO_2 in O_2 diffused continuously. Isometric tension changes were recorded from a Gould-Statham (UTC 2) force displacement transducer connected to a Beckman Type R

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Dynograph. For assay purposes initial maximal contractions were elicited with a high concentration of the contractile agonist [U-44069, 9.11-dideoxy-9 α ,11 α -epoxymethano PGF_{2 α}] and the tissue subsequently washed at intervals until tension returned to baseline. Agonist dose response curves were obtained using a cumulative-dose schedule (4-8 doses) and the preparations then washed at regular intervals until baseline tension was recorded. After an appropriate interval (1-1.5 hrs) agonist dose response curves were repeated in the presence of antagonist drug concentrations. Drug doses were delivered in 10 μ l volumes 5 minutes prior to the second agonist challenge, and cumulative agonist volumes did not exceed 100 μ l per bath. EC₅₀ values were obtained by regression analysis and used to calculate 'apparent' and Schild Plot pA₂ values by the method of Tallarida and Murray 1981.

Compounds of Formula I can be tested using the following assay to determine their mammalian leukotriene biosynthesis inhibiting activity.

Rat Peritoneal Polymorphonuclear (PMN)
Leukocyte Assay

Rats under ether anesthesia are injected (i.p.) with 8 ml of a suspension of sodium caseinate (6 grams in ca. 50 ml water). After 15-24 hr, the rats are sacrificed (CO₂) and the cells from the peritoneal cavity are recovered by lavage with 20 ml of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous

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shaking, filtered, through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500 μ l aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37°C, followed by the addition of 10 μ M A-23187. The suspension is stirred for an additional 4 minutes then bioassayed for LTB₄ content by adding an aliquot to a second 500 μ l portion of the PMN at 37°C. The LTB₄ produced in the first incubation causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of LTB₄ formation is calculated from the ratio of transmission change in the sample to the transmission change in the compound-free control.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay and are described in EP 140,684.

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In Table 4 below are presented data indicating the prostanoid antagonist activities of compounds of the present invention indicated in Table 1. It is to be noted that pA_2 values are on a
5 logerithmic scale, so that, for instance, a difference between two pA_2 values of 1 represents a difference in potency by a factor of 10.

Compounds A, B, C and D in Table 4 are known in the art: U.S. Patent 3,896,145 describes compounds
10 A and C, U.S. Patent 3,868,387 describes compound B, and compound D is described in U.S. Patent 3,905,998.

Compound A, which is a positional isomer of the novel compound 2, is nevertheless almost 12 times less potent as an inhibitor of platelet aggregation
15 and its pA_2 is a factor of 14 (antilog of 1.6) less than that of compound 2. The homolog B, with one carbon less than A, shows no significant activity. Also of interest is the fact that the fully aromatic carbazole analog of the novel compound 2, compound C,
20 does not possess any significant activity. Compounds D and E, isomeric with compound B further demonstrate that direct attachment of the carboxyl group to the tetrahydrocarbazole nucleus results in severe loss of activity.

25 Compound 8 indicates an interesting differentiation of prostaglandin antagonist activity, depending upon the tissue, with very weak action on the guinea pig trachea ($pA_2 < 6$), but with very good potency as an inhibitor of human platelet aggregation
30 ($IC_{50} = 0.09 \mu g/ml$).

Compound F demonstrates that a hydrogen atom attached to the 9-position (the nitrogen atom) results

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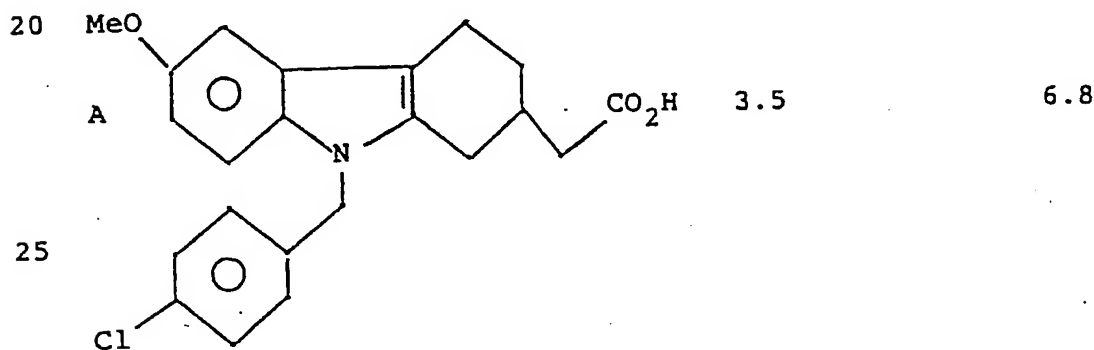
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in severe loss of activity. Likewise, compound G, with a 9-alkyl substituted, has almost completely lost activity. Compound H, with a 2-phenylethyl substituent at the 9-position has also suffered a serious loss of activity by the addition of a CH₂ group compared to Compound 1. The last three compounds (F, G and H) demonstrate the requirement for a benzyl or substituted benzyl group at position-9 in the compounds of the present invention.

10

Table 4Prostanoid Antagonist Activities

15	Compound	Inhibition of platelet aggregation (IC ₅₀ in µg/ml)	PA ₂
----	----------	--	-----------------

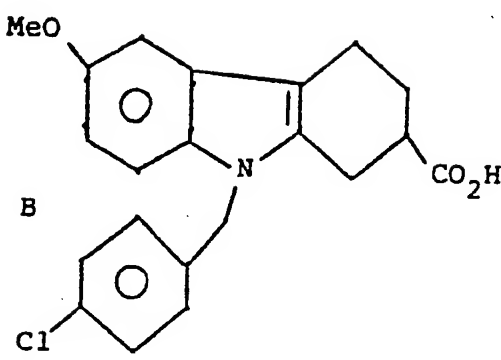
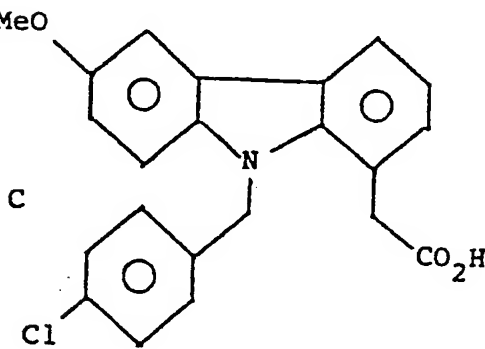
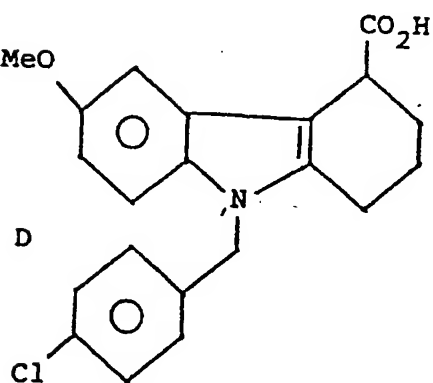


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Table 4 (Cont'd)

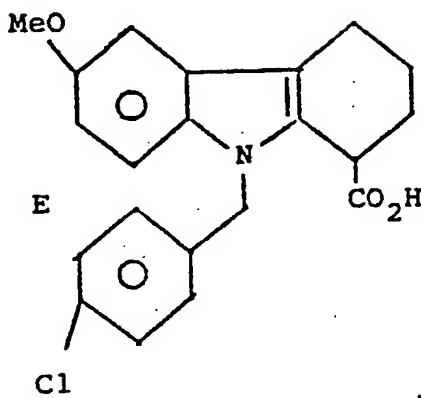
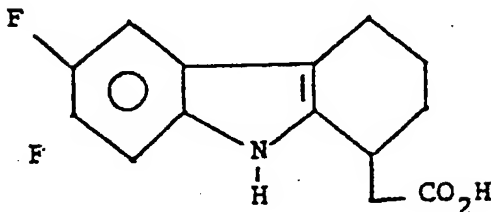
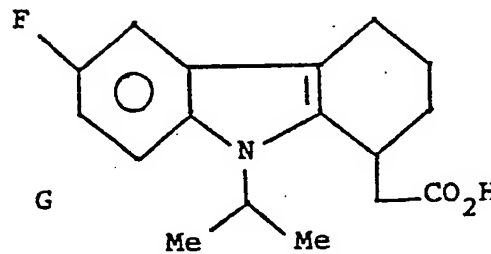
5		>30	< 6
10	B		
15		>30	6.58
20	C		
25			
30	D		< 6

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Table 4 (Cont'd)

5		4.23	6.66
15		3.41	< 6
20		13.6	< 6

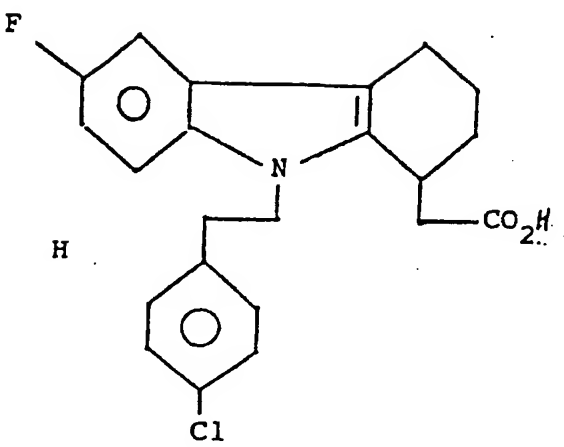
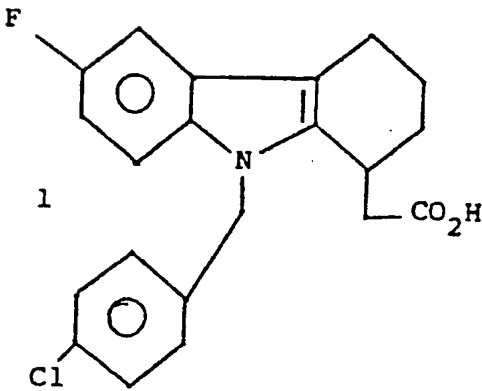
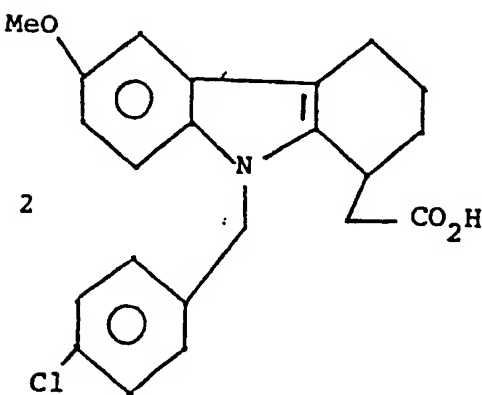
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Table 4 (Cont'd)

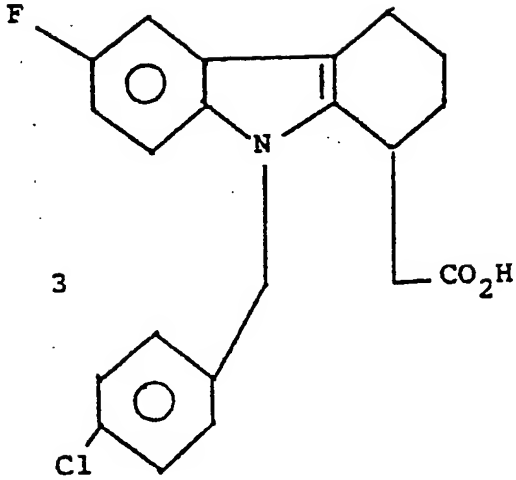
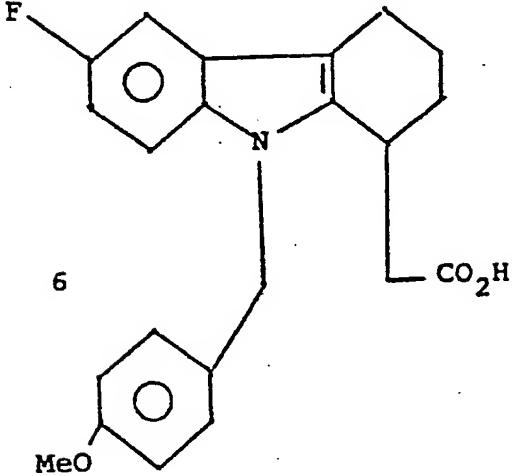
5		13.6	6.8
10			
15		0.03	8.6
20			
25			
30		0.30	8.4

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Table 4 (Cont'd)

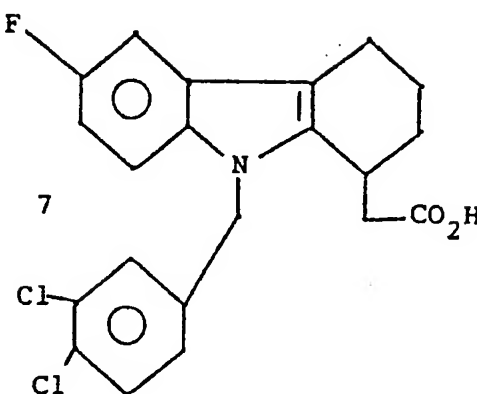
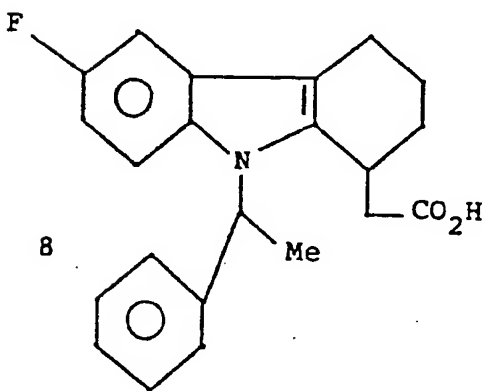
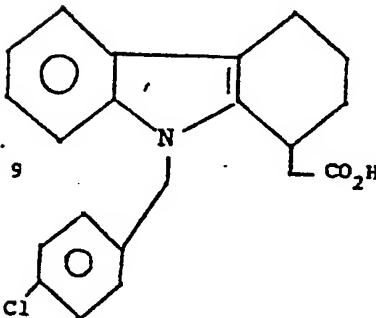
5		0.05	8.0
10	3		
15		0.15	8.7
20	6		
25			
30			

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Table 4 (Cont'd)

5		0.09	8.3
10			
15		0.09	< 6
20			
25		0.05	8.9
30			

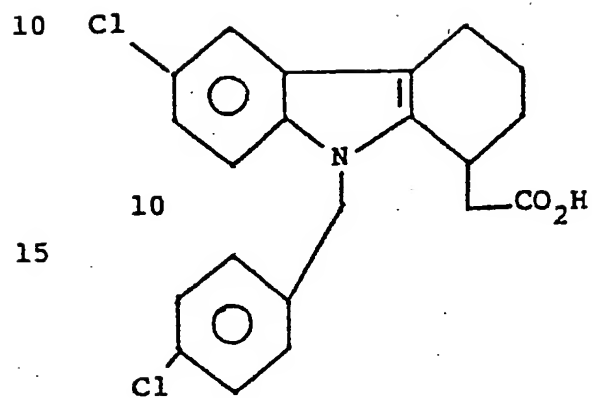
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Table 4 (Cont'd)

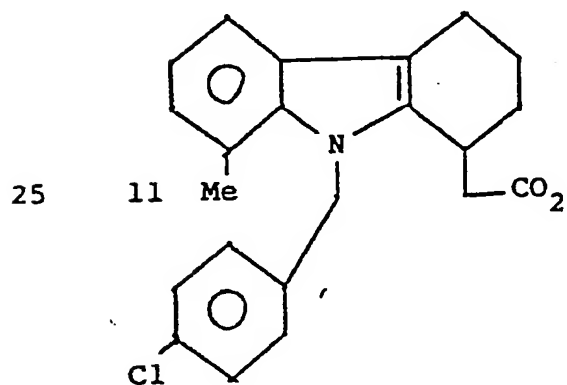
5



0.10

8.0

20



0.10

9.5

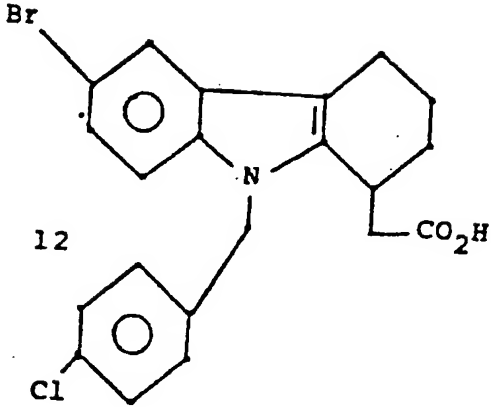
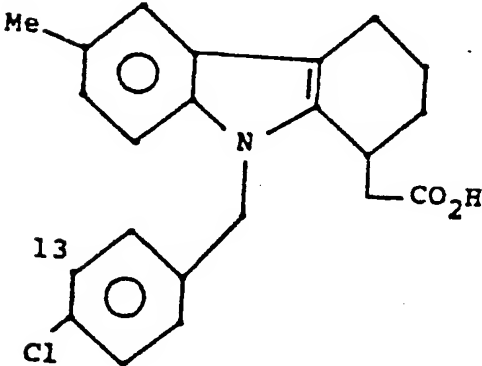
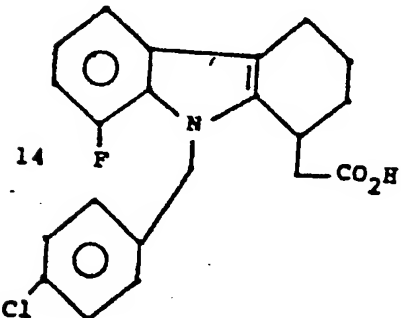
30

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Table 4 (Cont'd)

5		0.09	7.9
10			
15		0.08	7.6
20			
25			
30		0.08	9.4

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Table 4 (Cont'd)

5

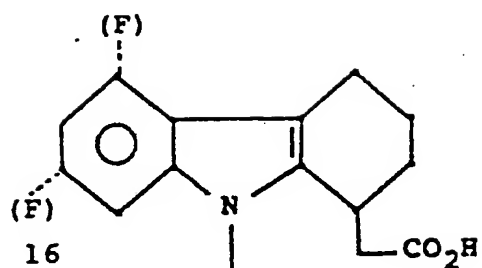
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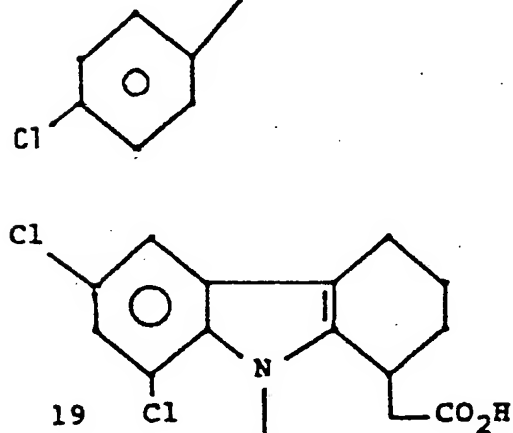
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30



0.17

8.9



0.07

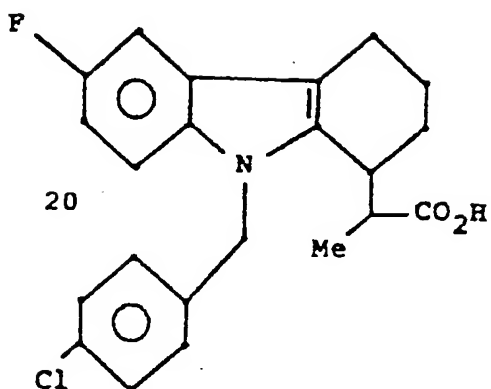
7.2

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Table 4 (Cont'd)

5		0.31	6.8
---	---	------	-----

The magnitude of a prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature or the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. In general, the daily dose range for anti-asthmatic, anti-allergic, or anti-thrombotic use lies within the range of from about 0.01 mg to about 100 mg per kg body weight of a mammal.

The exact amount of a compound of Formula I to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of use of a compound of Formula I to avoid future damage is co-administration with a non-steroidal anti-inflammatory drug (for example, indomethacin).

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The effective daily dosage level for compounds of Formula I inducing cytoprotection in mammals, especially humans, will generally range from about 0.002 mg/kg to about 100 mg/kg, preferably from about 0.02 mg/kg to about 30 mg/kg. The dosage may be administered in single or divided individual doses.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of Formula I. For example, oral, rectal, topical, parenteral, ocular, nasal, buccal, intravenous and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. The compositions include compositions suitable for oral, rectal, ophthalmic, pulmonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

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For use where a composition for intravenous administration is employed, a suitable dosage range for anti-asthmatic, or anti-allergic use is from about 0.01 mg to about 20 mg (preferably from about 0.1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.002 mg to about 100 mg (preferably from about 0.02 mg to about 30 mg and more preferably from about 0.1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day. In the case where an oral composition is employed, a suitable dosage range for anti-asthmatic, or anti-allergic use is, e.g. from about 1 to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 5 mg to about 40 mg per kg and for cytoprotective use from about 0.01 mg to about 100 mg (preferably from about 0.1 mg to about 30mg and were preferably from about 0.1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, or a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a suitable device. The preferred delivery system for inhalation in a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution in fluorocarbon propellants.

Suitable topical formulations of compound I include transdermal devices, aerosols, creams, ointments, lotions, dusting powder, and the like.

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In practical use, a compound of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques.

- 5 The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed,
- 10 such as, for example, water glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars,
- 15 microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets. Because of their ease of administration, tablets and
- 20 capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

- In addition to the common dosage forms set
- 25 out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosure of
- 30 which is hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be


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presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a
5 non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association
10 the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the
15 desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as
20 powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably,
25 each tablet contains from about 2.5 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 2.5 to about 500 mg of the active ingredient.

The following are examples of representative
30 pharmaceutical dosage forms for the compounds of Formula I:



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<u>Injectable Suspension (I.M.)</u>		<u>mg/ml</u>
	Compound of Formula I	2.0
	Methylcellulose	5.0
	Tween 80	0.5
5	Benzyl alcohol	9.0
	Benzalkonium chloride	1.0
Water for injection to a total volume of 1 ml		
<u>Tablet</u>		<u>mg/tablet</u>
10	Compound of Formula I	25.0
	Microcrystalline Cellulose	415.0
	Providone	14.0
	Pregelatinized Starch	43.5
	Magnesium Stearate	<u>2.5</u>
15		500
<u>Capsule</u>		<u>mg/capsule</u>
	Compound of Formula I	25.0
	Lactose Powder	573.5
20	Magnesium Stearate	<u>1.5</u>
		600

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac, diflunisal and the like, cyclooxygenase inhibitors, leukotriene antagonists, leukotriene biosynthesis inhibitors, H₂-receptor antagonists, antihistaminic agents, prostaglandin antagonists, ACE inhibitors, and thromboxane synthetase inhibitors.

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

5 Thus, for example, when a compound of the Formula I is combined with a second active ingredient the weight ratio of the compound of the Formula I to the second ingredient will generally range from about 1000:1 to about 1:1000, preferably from 200:1 to

10 1:200. Combinations of a compound of the Formula I and other active ingredients will generally be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

15 NSAIDs can be characterized into five groups:


- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives;

20 and

(5) the oxicams or a pharmaceutically acceptable salt thereof. NSAIDS which are within the scope of this invention are those disclosed in EP 140,684.

25 Pharmaceutical compositions comprising the Formula I compounds may also contain other inhibitors of the biosynthesis of the leukotrienes such as are disclosed in EP 138,481 (April 24, 1985), EP 115,394 (August 8, 1984), EP 136,893 (April 10, 1985), and EP

30 140,709 (May 8, 1985), which are hereby incorporated herein by reference.



The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP 106,565 (April 25, 1984) and EP 104,885 (April 4, 1984), which are hereby
5 incorporated herein by reference and others known in the art such as those disclosed in European Patent Application Nos. 56,172 and 61,800; and in U.K. Patent Specification No. 2,058,785, which are hereby incorporated herein by reference.

10 Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, other prostaglandin antagonists such as those disclosed in European Patent Application 11,067 (May 28, 1980) or other thromboxane antagonists
15 such as those disclosed in U.S. 4,237,160. They may also contain histidine decarboxyase inhibitors such as α -fluoromethyl-histidine, described in U.S. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1 or H_2 -receptor
20 antagonist, such as for instance benadryl, dramamine, histadyl, phenergan, terfenadine, acetamazole, cimetidine, ranitidine, famotidine, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981) and like compounds, such as those disclosed in U.S. Patent
25 Nos. 4,283,408; 4,362,736; 4,394,508; and a pending application, U.S.S.N. 301,616, filed September 14, 1981. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the
30 like. Compounds of I may also be usefully combined with most cell stabilizing agents, such as 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane and related

compounds described in British Patent Specifications 1,144,905 and 1,144,906. Another useful pharmaceutical composition comprises the Formula I compounds in combination with serotonin antagonists such as methysergide, the serotonin antagonists described in Nature, Vol. 316, pages 126-131, 1985, and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

When the second active ingredient in compositions of this invention is a thromboxane synthetase inhibitor, such inhibitor can be as described in UK 2,038,821 (e.g., UK 37248 and dazoxiben hydrochloride), U.S.P. 4,217,357 (e.g., UK 34787), U.S.P. 4,444,775 (e.g., CGS 13080), U.S.P. 4,226,878 (e.g., ONO 046), U.S.P. 4,495,357 (e.g., U63557A) U.S.P. 4,273,782 (e.g., UK-38485), or EP 98,690 (e.g., CV-4151).

An embodiment of the invention is a cardiovascular composition useful for treating arterial thrombosis which comprises an antithrombotic compound of the Formula I.

A further embodiment of the invention is a cardiovascular composition useful for treating arterial thrombosis which comprises: (i) the antithrombotic Formula I compound defined above; and, (ii) an angiotensin converting enzyme (ACE) inhibitor compound which is a member of the group: carboxyalkyl dipeptide derivatives; captopril [1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline]; 2-[N-(S)-1-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-cis,endo-2-azabicyclo[3,3,0]octane-3(S)-carboxylic acid; N-((S)-1-

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ethoxycarbonyl-3-phenylpropyl)-L-alanyl-N-(2-indanyl)-
glycine; 1-(N-[(S)-1-ethoxy-carbonyl-3-phenylpropyl]-
L-alanyl)-cis,syn-octahydro-(H-indole-2-S)-carboxylic
acid; 2-(N-[(S)-1-ethoxy-carbonyl-3-phenylpropyl]-L-
5 alanyl)-1,2,3,4-tetrahydro-iso-isoquinoline-3(S)-
carboxylic acid; and, 1-carboxy-methyl-3(S)-(1(S)-
ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-
1H[1]-benzazepine-2-one.

In particular the class of ACE inhibitors
10 which have been found to have a potentiating effect
when used in combination with the Formula I compounds
are those disclosed in U.S. Patent 4,374,829, which
also discloses methods for their preparation and
which patent is incorporated herein by reference. Of
15 the carboxyalkyl dipeptides disclosed in U.S. Patent
4,374,829, those of particular interest in this
invention are N-[1(S)-ethoxycarbonyl-3-phenyl-
propyl]-L-alanyl-L-proline, also known and referred
to herein as enalapril; N-[1(S)-carboxy-3-phenyl-
20 propyl]-L-alanyl-L-proline, also know and referred to
herein as enalapril diacid; and, N α -[1(S)-carboxy-
3-phenylpropyl]-L-lysyl-L-proline, also known and
referred to herein as lisinapril.

The combination composition of the invention
25 can contain varying amounts of (i) the Formula I
antithrombotic compound and (ii) ACE inhibitor
antihypertensive compounds. The weight ratio of
(i):(ii) can range from about 25 to 1; preferably
from about 10 to 1. In addition to the active
30 ingredients of (i) alone or of (i) and (ii) in
combination, the compositions of the invention can
also contain other conventional pharmaceutically

acceptable compounding ingredients, as necessary or desired. Such ingredients are generally referred to as carriers or diluents. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Whatever the dosage form, it will contain a pharmaceutically effective amount of the present composition.

The combination compositions can be administered orally or other than orally; e.g., parenterally, by insufflation, topically, rectally, etc.; using appropriate dosage forms; e.g., tablets, capsules, suspensions, solutions, and the like, for oral administration; suspension emulsions, and the like, for parenteral administration; solutions for intravenous administration; and ointments, transdermal patches, and the like, for topical administration. These compositions are formulated similarly to the compositions discussed above.

Treatment dosage for human beings for cardiovascular use can be varied as necessary. Generally, daily dosages of the composition of the invention can range from about 6000 to about 10 mg; preferably, from about 3000 to about 20 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form for cardiovascular use will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration may contain from 5 mg to 5 gm of active agents compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of

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the total composition. Dosage unit forms will generally contain between from about 20 mg to about 500 mg of active ingredients.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The composition of this invention inhibits platelet accumulation at the damaged endothelial surface via the Formula I compound. This inhibitory effect is potentiated by the presence of the antihypertensive compound.

Thus, the compositions of the invention are useful in treating thrombosis and are also of value in the management of acute and chronic congestive heart failure, and limitation of myocardial infarct damage.

In vivo testing of the composition of this invention in test animals (rabbits) can be used to demonstrate that this composition is pharmaceutically effective in decreasing platelet-related arterial thrombic formation.

To demonstrate the potentiation of the antihypertensive compound on the anti-thrombotic Formula I compound comprising the combination composition of the invention, the effect of these compounds on test animals (rabbits) can be determined separately and then in combination. The effect of a

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different class of antihypertensive agents singly and in combination with the Formula I compound of the invention can also be determined for comparative purposes. The methods employed are described in U.S. Patent 4,558,037 which is hereby incorporated herein by reference.

The following examples illustrate the preparation of the compounds of the present invention without, however, limiting the same thereto.

All temperatures are in degrees Celsius.

Reference Compounds

6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(4-fluorophenyl) hydrazine hydrochloride and ethyl-2-cyclohexanone acetate as starting materials, the title compound was prepared.

M.P. 124 -126°C

Reference Compounds

9-[1-(2-p-chlorophenyl)ethyl]-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 2, but using 1-[2-(4-chlorophenyl)ethyl]-1-(4-fluorophenyl) hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

Empirical Formula: $C_{22}H_{21}NFC1O_2$

C H N

Calculated	68.48	5.49	3.63
Found	68.15	5.70	3.65

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Reference Compounds

6-fluoro-9-isopropyl-1,2,3,4-tetrahydrocarbazol-1-yl-
acetic acid

5 Following the procedure of Example 1, but
using 1-(2-propyl)-1- (4-fluorophenyl)hydrazine
hydrochloride and ethyl 2-cyclohexanone acetate as
starting materials, the title compound was prepared.

Empirical Formula: $C_{17}H_{20}NFO_2$

M.P. 144-144.5 °C

10

Example 1

9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid

Step I

15 To 3.50 g of 1-(4-chlorobenzyl)-1-(4-fluoro-
phenyl)hydrazine hydrochloride in 70 cc of iso-
propanol was added 2.23 g of ethyl 2-cyclohexanone
acetate. The reaction was refluxed under nitrogen
for 16 hours. The resulting reaction mixture was
20 then evaporated to dryness and the residue suspended
in ether. The solid material was then filtered. The
ether filtrate was washed with water, dried and
evaporated. The resulting syrup was chromatographed
on silica gel to give 2.8 g (42%).

25

Step II

To 1.59 g of ethyl ester from step I in 10
cc of methanol was added 10 cc of water and 420 mg of
potassium hydroxide. The resulting solution was
30 refluxed for 4 hours. Upon cooling the reaction
mixture was then acidified with HCl (1N). The
resulting precipitate was filtered and washed with

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water. Analytically pure material was prepared by
trituration the solid with a mixture of hexane/ethyl
acetate (9:1) followed by filtration and drying on a
high vacuum pump to give 1.24 g of the title compound
5 (89%).

Analysis calculated for $C_{21}H_{19}NClFO_2$

	C	H	N	Cl	F
Calculated	67.83	5.15	3.77	9.53	5.11
Found	67.88	5.47	3.63	9.52	5.12

10

Example 2

3-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl]-propanoic acid

Following the procedure of Example 1, but
15 using 1-(4-chlorobenzyl)-1-(4-fluorophenyl)hydrazine
hydrochloride and methyl-2-cyclohexanone propionate
as starting materials, the title compound was
prepared.

Empirical formula: $C_{22}H_{21}ClFNO_2$

20

	C	H	N
Calculated	68.48	5.49	3.63
Found	68.26	5.57	3.60

Example 3

25 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydro-
carbazol-1-yl]-propanoic acid

Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(4-methoxyphenyl)hydrazine
hydrochloride and methyl-2-cyclohexanone propionate
30 as starting materials, the title compound was
prepared.

Empirical formula: $C_{22}H_{22}ClNO_3$

	C	H	N	Cl
Calculated	69.43	6.08	3.52	8.91
Found	69.24	5.98	3.60	8.85

5

Example 4

9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but
10 using 1-(4-chlorobenzyl)-1-(4-methoxyphenyl)hydrazine hydrochloride and ethyl-2-cyclohexanone acetate as starting materials, the title compound was prepared.

M.P. 152-153°C.

15

Example 5

2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl]ethanol

1.10 g of 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ethyl ester was
20 dissolved in 500 ml dry tetrahydrofuran and the reaction was cooled at 0°C and one equivalent of lithium aluminium hydride (LAH) was added portion wise. The reaction was allowed to warm up to room temperature and stirred for 16 hrs. The reaction
25 mixture was quenched with NH_4Cl (aq.). Ethyl acetate was added (100 ml) and the organic phase separated, washed with water and brine, dried and evaporated. The product was isolated by column chromatography.

30 M.P. 98.0 - 98.5 °C.

Example 6

3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydro-
carbazol-1-yl]-propanol

5 Following the procedure of Example 5, but
using 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetra-
hydrocarbazol-1-yl]-propanoic acid methyl ester from
Example 3 as starting material, the title compound
was prepared.

Empirical formula: $C_{23}H_{26}ClNO_2$

10		C	H	N
	Calculated	71.95	6.83	3.65
	Found	71.86	6.65	3.81

Example 7

15 (-)-9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Step I

10.0 g of 9-p-chlorobenzyl-6-fluoro-1,2,3,4-
tetrahydrocarbazol-1-yl-acetic acid from Example 1 was
20 dissolved in a mixture of hot (refluxing) aceto-
nitrile (150 cc), and ethanol (25cc) and 4.4 g of
d(+) ephedrine was added. The reflux was continued
for 15 min. and the hot solution was filtered and
allowed to cool to room temperature. Crystals
25 separated from the solution and were separated by
filtration. After three recrystallizations from
acetonitrile 3.9 g of the pure salt was obtained.

Step II

30 3.9 g of pure salt from step I was dissolved
in 200 cc of methanol and acidified using 1 N hydro-
chloric acid. Water was added and the crystals were

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separated by filtration and dried under vacuum. Upon trituration with hexane ethyl acetate mixture (9:1) the title compound was prepared.

$\alpha_D = -42.5$ (methanol) M.P. 151 - 151.5°C.

5

Example 8

(+)-9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-carbazol-1-yl-acetic acid

Following the method of Example 7, but using 1(-) ephedrine and 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid as starting material, the title compound was prepared.

$\alpha_D = +43.0$ (methanol) M.P. 150 - 150.5°C.

15

Example 9

9-benzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(benzyl)-1-(4-fluorophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

Analysis calculated for $C_{21}H_{20}NFO_2$

	C	H	N
Calculated	74.76	5.98	4.15
25 Found	74.95	6.07	3.90

Example 10

9-p-methoxybenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(4-methoxybenzyl)-1-(4-fluorophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

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Analysis calculated for $C_{22}H_{22}NFO_3$

	C	H	N
Calculated	71.92	6.04	3.91
Found	71.70	6.22	4.05

5

Example 11

9-(3,4-dichloro)benzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the procedure of Example 1, but
10 using 1-(3,4-dichlorobenzyl)-1-(4-fluorophenyl)
hydrazine hydrochloride and ethyl 2-cyclohexanone
acetate as starting materials, the title compound was
prepared.

Analysis calculated for $C_{21}H_{18}NCl_2FO_2$.

	C	H	N
Calculated	62.08	4.47	3.45
Found	61.96	4.71	3.67

15

Example 12

20 9-[1-(1-phenyl)ethyl]-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the procedure of Example 1, but
using 1-[1-(1-phenyl)ethyl]-1-(4-fluorophenyl)-
hydrazine hydrochloride and ethyl 2-cyclohexanone
25 acetate as starting materials, the title compound was
prepared.

	C	H	N	F
Calculated	75.19	6.31	3.99	5.41
Found	75.18	6.05	4.11	5.51

30

Example 13

9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic
acid

Following the procedure of Example 1, but
5 using 1-(4-chlorobenzyl)-1-(phenyl)hydrazine hydro-
chloride and ethyl 2-cyclohexanone acetate as starting
materials, the title compound was prepared.

Empirical Formula: $C_{21}H_{20}NClO_2$

	C	H	N	Cl
10 Calculated	71.28	5.70	3.96	10.02
Found	70.7n	5.90	3.82	10.23

Example 14

9-p-chlorobenzyl-6-chloro-1,2,3,4-tetrahydrocarbazol-
15 1-yl-acetic acid

Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(4-chlorophenyl)hydrazine .
hydrochloride and ethyl-2-cyclohexanone acetate as
starting materials, the title compound was prepared.

20 Empirical Formula: $C_{21}H_{19}NCl_2O_2$

	C	H	N	Cl
Calculated	69.96	4.93	3.61	18.26
Found	65.20	5.16	3.38	18.04

25 Example 15

9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid

Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(2-methylphenyl)hydrazine
30 hydrochloride and ethyl-2-cyclohexanone acetate as
starting materials, the title compound was prepared.

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Empirical Formula: $C_{22}H_{22}NClO_2$

	C	H	N	Cl
Calculated	71.83	6.03	3.81	9.64
Found	72.19	6.23	4.12	9.84

5

Example 16

6-bromo-9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(4-bromophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

Empirical formula: $C_{21}H_{19}BrClNO_2$

	C	H	N	Br	Cl
Calculated	58.29	4.43	3.24	18.46	8.19
Found	58.49	4.60	3.44	18.50	8.27

15

Example 17

9-p-chlorobenzyl-6-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(4-methylphenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

25 Empirical formula: $C_{22}H_{22}ClNO_2$

	C	H	N	Cl
Calculated	71.83	6.03	3.81	9.64
Found	71.72	6.14	3.77	9.88

30

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Example 18

2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl]propanoic acid.

Following the procedure of Example 1, but
5 using 1-(4-chlorobenzyl)-1-(4-fluorophenyl) hydrazine
hydrochloride and methyl 2-(2-cyclohexanone) pro-
pionate as starting materials, the title compound was
prepared.

M.P. 203-205°C

10

Example 19

9-p-chlorobenzyl-8 fluoro-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid.

Following the procedure of Example 1, but
15 using 1-(4-chlorobenzyl)-1-(2-fluorophenyl) hydrazine
hydrochloride and ethyl 2-cyclohexanone acetate as
starting materials, the title compound was prepared.

M.P. 228-229°C.

20

Example 20

3-[(α and β)-t-butyl-6-fluoro-9-(p-chlorobenzyl)-
1,2,3,4-tetrahydrocarbazol-1-yl]acetic acid.

Following the procedure of Example 1 but
using 4-t-butyl-2-carbomethoxymethyl cyclohexanone
25 and 1-(4-chlorobenzyl)-4-fluorophenylhydrazine hydro-
chloride as the starting materials, the title compound
was prepared.

M.P. 210-211°C.

30

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Example 21

9-p-chlorobenzyl-5-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid and 9-p-chlorobenzyl-7-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (mixture).

5 Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(3-fluorophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compounds were prepared.

Empirical Formula: $C_{21}H_{19}NClFO_2$

10 M.P. 211-219°C

Example 22

9-p-chlorobenzyl-5,7-dichloro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

15 Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(3,5-dichlorophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

20 Empirical formula: $C_{21}H_{18}NCl_3O_2$

M.P. 204-206°C

Example 23

25 9-p-chlorobenzyl-6,8-dichloro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

30 Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(2,4-dichlorophenyl)hydrazine hydrochloride and ethyl 2-cyclohexanone acetate as starting materials, the title compound was prepared.

Empirical formula: $C_{21}H_{18}NCl_3O_2$

M.P. 203-204°C.

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Example 24

9-p-Chlorobenzyl-6-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid

5 Following the procedure of Example 1, but
using 1(4-chlorobenzyl)-1-(4-isopropylphenyl)-
hydrazine hydrochloride and ethyl 2-cyclohexanone
acetate as starting material, the title compound was
prepared.

Empirical Formula: $C_{24}H_{26}ClNO_2$

	C	H	N	Cl
10 Calc:	72.81	6.62	3.54	8.95
Found:	72.83	7.09	3.61	9.21

Example 25

15 9-p-Chlorobenzyl-6-tert-butyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid

Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(4-tert-butylphenyl)
hydrazine hydrochloride and ethyl 2-cyclohexanone
20 acetate as starting materials, the title compound was
prepared.

Empirical Formula: $C_{25}H_{28}ClNO_2$

	C	H	N	Cl
Calc.	73.24	6.88	3.42	8.65
25 Found:	73.21	7.32	3.10	8.26

Example 26

9-p-Chlorobenzyl-6-trifluoromethyl-1,2,3,4-tetra-
hydrocarbazol-1-yl-acetic acid

30 Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(4-trifluoromethylphenyl)
hydrazine hydrochloride and ethyl 2-cyclohexanone

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acetate as starting materials, the title compound was prepared. m.p. 167-168°C.

Example 27

5 9-p-Chlorobenzyl-6-methylthio-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the procedure of Example 1, but using 1-(4-chlorobenzyl)-1-(4-methylthiophenyl) hydrazine hydrochloride and ethyl 2-cyclohexanone
10 acetate as starting materials, the title compound was prepared.

Empirical Formula: $C_{22}H_{22}ClNO_2S$

	C	H	N	S	Cl
Calc:	66.07	5.54	3.50	8.02	8.86
15 Found:	66.27	5.83	3.38	8.00	8.70

Example 28

9-p-Chlorobenzyl-6-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

20 Step I

To 498 mg of ethyl 9-p-chlorobenzyl-6-methylthio-1,2,3,4-tetrahydrocarbazol-1-yl-acetate from Example 27, Step I, in 10 cc of methylene chloride was added 300 mg of m-chloro perbenzoic acid. The
25 resulting mixture was stirred for 1.5 hours at room temperature. The reaction mixture was diluted with ether and washed consecutively with a solution of sodium bicarbonate, water and brine. The crude product obtained after evaporation of the organic
30 layer was purified on silica gel by flash chromatography eluting with 20% hexane/ethyl acetate and yielded 420 mg (82%) of the pure sulfoxide derivative.

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Step II

Following the procedure of Example 1, Step II, but using the ethyl ester from Step I, there was obtained the title compound. m.p. 105-107°C.

5 Empirical Formula: $C_{22}H_{22}ClNO_3S$

	C	H	N	S	Cl
Calc:	63.53	5.33	3.37	7.71	8.52
Found:	63.31	5.03	2.94	7.69	8.48

10

Example 29

9-p-Chlorobenzyl-6-methylsulfonyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Step I

To 439 mg of ethyl 9-p-chlorobenzyl-6-methyl-
15 sulfinyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetate from
Example 28, Step I, in 10 cc of methylene chloride
was added 353 mg of m-chloro perbenzoic acid. The
resulting mixture was stirred for 18 hours at room
temperature. The reaction mixture was diluted with
20 ether and washed consecutively with a solution of
sodium bicarbonate, water and brine. The crude
product obtained after evaporation of the organic
layer was purified on silica gel by flash chromato-
graphy eluting with 30% hexane/ethyl acetate and
25 yielded 200 mg (42%) of the pure sulfone derivative.

Step II

Following the procedure of Example 1, Step
II, but using the ethyl ester from Step I, there was
30 obtained the title compound. m.p. 101-102°C.

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Example 30

9-p-Chlorobenzyl-8-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid

5 Following the procedure of Example 1, but
using 1-(4-chlorobenzyl)-1-(2-isopropylphenyl)
hydrazine hydrochloride and ethyl 2-cyclohexanone
acetate as starting materials, the title compound was
prepared.

Empirical Formula: $C_{24}H_{26}ClNO_2$

10

	C	H
Calc:	72.81	6.62
Found:	72.59	6.90

Example 31

15 9-p-Chlorobenzyl-8-methylthio-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid

Following the procedure of Example 34, but
using 1-(2-methylthiophenyl) hydrazine hydrochloride
and ethyl 2-cyclohexanone acetate as starting
20 materials, the title compound was prepared. m.p.
141-142°C.

Example 32

25 9-p-Chlorobenzyl-8-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the procedure of Example 28, but
using the ethyl ester from Example 31, Step II, there
was obtained the title compound. m.p. 119-120.5°C.

30

Example 33

9-p-Chlorobenzyl-6-fluoro-3-methyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the procedure of Example 1, but
5 using 1-(4-chlorobenzyl)-1-(4-fluorophenyl) hydrazine
hydrochloride and ethyl 4-methyl-2-cyclohexanone
acetate as starting materials, the title compound was
prepared. m.p. 205-206°C.

Empirical Formula: $C_{22}H_{21}FClNO_2$

10		C	H	N	Cl
	Calc:	68.48	5.49	3.63	9.19
	Found:	68.80	5.50	3.30	9.47

Example 34

15 9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Step I

To 114 g of 1-(2,4-difluorophenyl) hydrazine
hydrochloride in 350 cc of 2-propanol containing 40
20 cc of acetyl chloride was added 138 g of ethyl
2-cyclohexanone acetate. The reaction was refluxed
under nitrogen for 2 days. After cooling, 200 cc of
ether was added and the precipitate filtered. The
filtrate was evaporated to dryness. The resulting
25 residue was dissolved in a (1:1) mixture of
ether/ethyl acetate and consecutively washed with
water, sodium bicarbonate solution and brine. The
organic layer was dried over sodium sulfate and
evaporated to dryness. The crude product was passed
30 through a silica gel bed eluting with 5% ethyl
acetate/hexane to yield 84 g of a 1:2 mixture of
ethyl and isopropyl esters.

Step II

84 g of esters from Step I was dissolved in 250 cc of methanol and 400 cc of sodium hydroxide (1N) was added and refluxed 4 hours. After cooling, the reaction mixture was washed with a (1:1) mixture of ether/hexane and the aqueous layer was acidified with HCl (1N). The resulting precipitate was filtered, washed with water and air dried to afford 50 g of 6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

Step III

A solution of 11:1 g of acid from Step II in 100 cc of THF was added portionwise 10.3 g of potassium tert-butoxide. The resulting mixture was stirred for 45 min. at room temperature and 10.3 g p-chlorobenzyl bromide was added portionwise. The reaction mixture was stirred 18 hours at room temperature. The resulting mixture was diluted with 100 cc of water and washed with hexane. The aqueous layer was acidified with HCl (1N) and the resulting precipitate filtered washed with water and air-dried to afford 9.4 g of the title compound. m.p. 168.5-170°C.

25

Example 35

9-p-Chlorobenzyl-6,8-dimethyl-1,2,3,4-tetrahydro-carbazol-1-yl-acetic acid

Following the procedure of Example 34, but using 1-(2,4-dimethylphenyl) hydrazine hydrochloride and ethyl 2-cyclohexanone acetate in Step I as starting materials, the title compound was prepared. m.p. 187-188°C.

Example 36

9-p-Chlorobenzyl-6-methoxy-8-methyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

5 Following the procedure of Example 34, but
using 1-(4-methoxy-2-methylphenyl) hydrazine
hydrochloride and ethyl 2-cyclohexanone acetate as
starting materials, the title compound was
prepared. m.p. 188-188.5°C.

Example 37

10 (-)-9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

15 Following the method of Example 7, but using
d(+)-ephedrine and 9-p-chlorobenzyl-6,8-difluoro-
1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid from
Example 34 as starting materials, the title compound
was prepared. from Example 34 $[\alpha]_D = -64.3^\circ$
(methanol) m.p. 130-131°C.

Example 38

20 (+)-9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

25 Following the method of Example 37, but
using 1(-)-ephedrine, the title compound was prepared.
 $[\alpha]_D = +61.5^\circ$ (methanol) m.p. 129.5-130°C.

Example 39

30 (-)-9-p-Chlorobenzyl-8-methyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid

Following the method of Example 7, but using
d(+)-ephedrine and 9-p-chlorobenzyl-8-methyl-1,2,3,4-
tetrahydrocarbazol-1-yl-acetic acid from Example 15

as starting materials, the title compound was prepared. $[\alpha]_D = -51.6^\circ$ (methanol) m.p. 196-198°C.

5

Example 40

(+)-9-p-Chlorobenzyl-8-methyl-1,2,3,4-tetrahydro-carbazol-1-yl-acetic acid

Following the method of Example 39, but using 1(-)ephedrine, the title compound was prepared.

10

$[\alpha]_D = +45.9^\circ$ (methanol) m.p. 195-197°C.

Example 41

(-)-9-p-Chlorobenzyl-8-fluoro-1,2,3,4-tetrahydro-carbazol-1-yl-acetic acid

15

Following the method of Example 7, but using d(+)ephedrine and 9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid from Example 19 as starting materials, the title compound was prepared. $[\alpha]_D = -62.1^\circ$ (methanol) m.p. 74-75°C.

20

Example 42

(+)-9-p-Chlorobenzyl-8-fluoro-1,2,3,4-tetrahydro-carbazol-1-yl-acetic acid

Following the method of Example 41, but using 1(-)ephedrine, the title compound was prepared. $[\alpha]_D = +65.2^\circ$ (methanol) m.p. 94-94.5°C.

25

Example 43

2-(9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-carbazol-1-yl)ethanol

30

Following the procedure of Example 5, but using a mixture of 9-p-chlorobenzyl-6,8-difluoro-

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1,2,3,4-carbazol-1-yl-acetic acid ethyl and isopropyl esters from Example 34 as starting materials, the title compound is obtained.

5

Example 44

(-) or (+) 2-(9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl)ethanol

Following the procedure of Example 5, but using (-) or (+) 9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid from Example 37 or 38 as starting material, the title compounds are obtained.

15

20

25

30

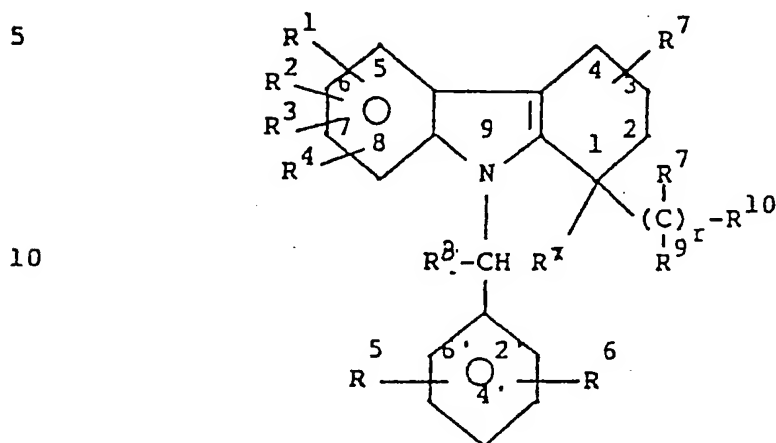
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CLAIMS for the contracting states BE, FR, DE, GB, NL, IT, LU, SE, CH

1. A compound of the formula:



I

wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently selected from:

- 20
- (1) hydrogen;
 - (2) alkyl having 1 to 6 carbon atoms;
 - (3) alkenyl having 2 to 6 carbon atoms;
 - (4) $-(CH_2)_n M$

wherein n is 0 to 3 and M is

- 25
- a) OR^{13} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{13} ;
 - e) phenyl or substituted phenyl
- 30
- wherein substituted phenyl is as defined below in the definition of R^{13} ;

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- 5
- f) COOR^{14} ;
- g) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{R}^{15} \end{array}$;
- h) tetrazole;
- i) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}^{16} \end{array}$ wherein R^{16} is C_1 to C_6 alkyl, benzyl or phenyl;
- 10 j) $-\text{NR}^{14}\text{R}^{14}$;
- k) $-\text{NHSO}_2\text{R}^{17}$ wherein R^{17} is C_1 to C_6 alkyl, 4-methylphenyl, phenyl, or CF_3 ;
- 15 l) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH}_2\text{OH} \end{array}$;
- m) $-\text{SOR}^{13}$;
- n) $-\text{CONR}^{14}\text{R}^{14}$;
- o) $-\text{SO}_2\text{NR}^{14}\text{R}^{14}$;
- p) $-\text{SO}_2\text{R}^{13}$;
- 20 q) NO_2 ;
- r) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{R}^{15} \end{array}$;
- s) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{NR}^{14}\text{R}^{14} \end{array}$;
- 25 t) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{OR}^{16} \end{array}$;
- u) CN ;
- v) N_3 ;
- 30 R^7 is H or alkyl of 1 to 6 carbons;
- R^8 is H or alkyl of 1 to 6 carbon atoms;
- each R^9 is independently H, OH, C_1 to $\text{C}_4=\text{O}$ -alkyl or alkyl of 1 to 4 carbons;

R^{10} is COOH; CH_2OH ; CHO; tetrazole;
NHSO₂ R^{11} wherein R^{11} is OH, alkyl or alkoxy of
1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,
phenyl or phenyl substituted by alkyl or alkoxy
5 groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN,
formyl or acyl to 1 to 6 carbons; CONHSO₂ R^{11} ;
hydroxymethylketone; CN; or CON(R^9)₂;

r is 1 to 6;

each R^{13} independently is H; C_1 to C_6
10 alkyl; benzyl; phenyl or substituted phenyl wherein
the substituents are C_1 to C_3 alkyl, halogen, CN,
 CF_3 , COOR¹⁴, CH_2 COOR¹⁴, C_1 to C_3 alkoxy,
or C_1 to C_4 perfluoroalkyl;

each R^{14} is independently H, phenyl,
15 benzyl or C_1 to C_6 alkyl; and,

each R^{15} independently is H,
(CH_2)_mCOOR¹⁴ wherein m is 0 to 4, C_1 to C_6
alkyl, CF_3 , phenyl, or substituted phenyl wherein
substituted phenyl is as defined above in the
20 definition of R^{13} ;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 which is:
- 25 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
- 3-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl]-propanoic acid;
- 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl]-propanoic acid;
- 30 9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
- 2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl]-1 ethanol;
- 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl]-propanol;
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- (-)9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
(+)9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
5 9-benzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-
acetic acid;
9-p-methoxybenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid;
9-(3,4-dichloro)benzyl-6-fluoro-1,2,3,4-tetrahydro-
10 carbazol-1-yl-acetic acid;
9-[1-(1-phenyl)ethyl]-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic
acid;
15 9-p-chlorobenzyl-6-chloro-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;
9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;
6-bromo-9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-
20 yl-acetic acid;
9-p-chlorobenzyl-6-methyl-1,2,3,4-tetrahydrocarbazol-1-
yl acetic acid;
2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol
-1-yl-]propanoic acid;
25 9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid;
3-[(α and β)-t-butyl-6-fluoro-9-(p-chlorobenzyl)-
1,2,3,4-tetrahydrocarbazol-1-yl]acetic acid;
9-p-chlorobenzyl-5-fluoro-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;
9-p-chlorobenzyl-7-fluoro-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;

- 9-p-chlorobenzyl-5,7-dichloro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6,8-dichloro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid.
- 5 9-p-chlorobenzyl-6-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-tert-butyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-trifluoromethyl-1,2,3,4-tetra-
10 hydrocarbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methylthio-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 15 9-p-chlorobenzyl-6-methylsulfonyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-methylthio-1,2,3,4-tetrahydrocar-
20 bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-fluoro-3-methyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 25 9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6,8-dimethyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methoxy-8-methyl-1,2,3,4-tetrahydro-
30 carbazol-1-yl-acetic acid;
- (-)-9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;

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- (+)-9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(-)-9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
5 (+)-9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(-)-9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(+)-9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
10 2-(9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl)ethanol;
(-) or (+) 2-(9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl)ethanol.

15

3. A compound according to Claim 1, which

is:

- 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
20 9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.
25

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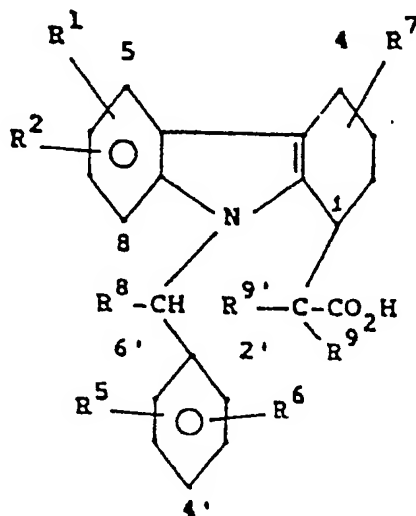
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4. A compound according to Claim 1, which is:

- (-)-9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
5 (-)-9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
(-)-9-p-Chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
10 (-)-9-p-Chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid.

5. A compound of the formula:



wherein:

	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
5	1 (Ex. 1)	6-F	H	4'-Cl	H	H, H	H	H
	2 (Ex. 4)	6-OMe	H	4'-Cl	H	H, H	H	H
	3 (Ex. 7)	6-F	H	4'-Cl	H	H, H	H	H
10	(-) isomer							
	4 (Ex. 8)	6-F	H	4'-Cl	H	H, H	H	H
	(+) isomer							
15	5 (Ex. 9)	6-F	H	H	H	H, H	H	H
	6 (Ex. 10)	6-F	H	4'-OMe	H	H, H	H	H
	7 (Ex. 11)	6-F	H	3'-Cl	4'-Cl	H, H	H	H
20	8 (Ex. 12)	6-F	H	H	H	H, H	H	Me
	9 (Ex. 13)	H	H	4'-Cl	H	H, H	H	H
25	10 (Ex. 14)	6-Cl	H	4'-Cl	H	H, H	H	H
	11 (Ex. 15)	8-Me	H	4'-Cl	H	H, H	H	H
	12 (Ex. 16)	6-Br	H	4'-Cl	H	H, H	H	H
30	13 (Ex. 17)	6-Me	H	4'-Cl	H	H, H	H	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	14 (Ex. 19)	8-F	H	4'-Cl	H	H, H	H	H
5	15 (Ex. 20)	6-F	H	4'-Cl	H	H, H	3-t-Bu	H
	16 (Ex. 21)	5-F	H	4'-Cl	H	H, H	H	H
	17 (Ex. 21)	7-F	H	4'-Cl	H	H, H	H	H
10	18 (Ex. 22)	5-Cl	7-Cl	4'-Cl	H	H, H	H	H
	19 (Ex. 23)	6-Cl	8-Cl	4'-Cl	H	H, H	H	H
15	20 (Ex. 18)	6-F	H	4'-Cl	H	Me, H	H	H
	21	6-F	H	4'-Cl	H	Me, Me	H	H
	22	6-F	H	4'-Cl	H	H, H	1-Me	H
20	23	8-Br	H	4'-Cl	H	H, H	H	H
	24 (Ex. 24)	6-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
25	25 (Ex. 25)	6-C(Me) ₃	H	4'-Cl	H	H, H	H	H
	26 (Ex. 26)	6-CF ₃	H	4'-Cl	H	H, H	H	H
	27 (Ex. 27)	6-SMe	H	4'-Cl	H	H, H	H	H
30	28 (Ex. 28)	6-S(O)Me	H	4'-Cl	H	H, H	H	H
	29 (Ex. 29)	6-S(O) ₂ Me	H	4'-Cl	H	H, H	H	H

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Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
30 (Ex. 30)	8-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
5 31 (Ex. 31)	8-SMe	H	4'-Cl	H	H, H	H	H
32 (Ex. 32)	8-S(0)Me	H	4'-Cl	H	H, H	H	H
33 (Ex. 33)	6-F	H	4'-Cl	H	H, H	3-Me	H
10 34 (Ex. 34)	6-F	8-F	4'-Cl	H	H, H	H	H
35 (Ex. 35)	6-Me	8-Me	4'-Cl	H	H, H	H	H
15 36 (Ex. 36)	6-OMe	8-Me	4'-Cl	H	H, H	H	H
37 (Ex. 37)	6-F(-)Isomer	8-F	4'-Cl	H	H, H	H	H
38 (Ex. 38)	6-F(+)Isomer	8-F	4'-Cl	H	H, H	H	H
20 39 (Ex. 39)	8-Me(-)Isomer	H	4'-Cl	H	H, H	H	H
40 (Ex. 40)	8-Me(+)Isomer	H	4'-Cl	H	H, H	H	H
25 41 (Ex. 41)	8-F(-)Isomer	H	4'-Cl	H	H, H	H	H
42 (Ex. 42)	8-F(+)Isomer	H	4'-Cl	H	H, H	H	H
43	6-F	8-F	3'-Cl	4'-Cl	H, H	H	H
30 44	6-F	8-F	2'-Cl	4'-Cl	H, H	H	H

Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
45	6-F	8-F	4'-OMe	H	H, H	H	H
5 46	6-F	8-F	4'-OH	H	H, H	H	H
47	6-F	8-F	4'-SMe	H	H, H	H	H
48	6-F	H	4'-S(O)Me	H	H, H	H	H
10 49	6-F	8-F	4'-NHCOMe	H	H, H	H	H
50	6-F	H	4'-S(O) ₂ Me	H	H, H	H	H
15 51	6-F	H	4'-F	H	H, H	H	H
52	6-F	H	4'-Br	H	H, H	H	H
53	6-F	8-Me	4'-Cl	H	H, H	H	H
20 54	6-F	H	4'-CO ₂ H	H	H, H	H	H
55	6-F	H	4'-CO ₂ Me	H	H, H	H	H
25 56	6-F	8-F	4'-n-C ₃ H ₇	H	H, H	H	H
57	6-F	8-F	3'-I	4'-OH	H, H	H	H
58	6-F	8-F	4'-I	H	H, H	H	H
30 59	6-N ₃	H	4'-Cl	H	H, H	H	H
60	6-F	H	4'-N ₃	H	H, H	H	H

6. The use of a compound as claimed in claim 1 for the manufacture of a medicament for inhibiting leukotriene synthesis in a mammal.

5 7. The use of a compound as claimed in claim 1 for the manufacture of a medicament for antagonizing prostaglandins in mammals.

8. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 9. A pharmaceutical composition which comprises a compound of Claim 1 and an effective amount of a second active ingredient selected from the group consisting of non-steroidal anti-inflammatory drugs; peripheral analgesic
15 agents; cyclooxygenase inhibitors; leukotriene antagonists; leukotriene biosynthesis inhibitors; H₁-receptor antagonists; H₂ receptor antagonists; prostaglandin antagonists; ACE inhibitors, or thromboxane synthetase inhibitors.

20 10. A pharmaceutical composition according to Claim 9, wherein the second active ingredient is indomethacin.

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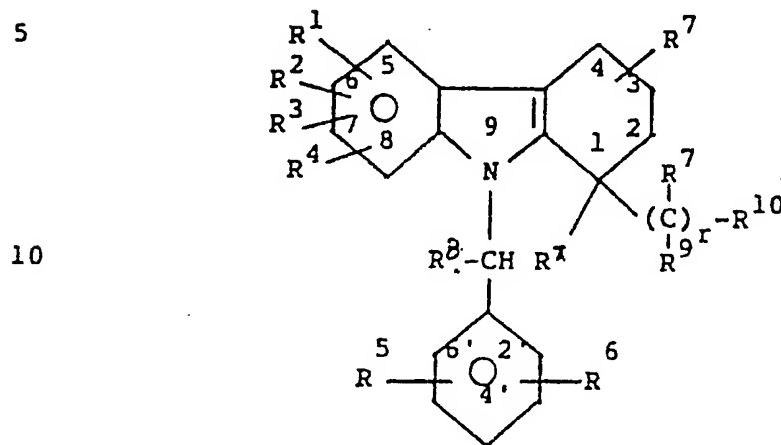
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CLAIMS for the contracting states AT, GR, ES.

1. A process for the preparation of a compound of the formula:



I

wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are
each independently selected from:

- 20
- (1) hydrogen;
 - (2) alkyl having 1 to 6 carbon atoms;
 - (3) alkenyl having 2 to 6 carbon atoms;
 - (4) $-(CH_2)_n M$

wherein n is 0 to 3 and M is

- 25
- a) OR^{13} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{13} ;
 - e) phenyl or substituted phenyl
wherein substituted phenyl is
as defined below in the
definition of R^{13} ;
- 30

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- 5 f) COOR^{14} ;
- g) $\overset{\text{O}}{\parallel} \text{-C-R}^{15}$;
- h) tetrazole;
- i) $\overset{\text{O}}{\parallel} \text{-NH-C-R}^{16}$ wherein R^{16} is C_1 to C_6 alkyl, benzyl or phenyl;
- 10 j) $\text{-NR}^{14}\text{R}^{14}$;
- k) $\text{-NHSO}_2\text{R}^{17}$ wherein R^{17} is C_1 to C_6 alkyl, 4-methylphenyl, phenyl, or CF_3 ;
- 15 l) $\overset{\text{O}}{\parallel} \text{-C-CH}_2\text{OH}$;
- m) -SOR^{13} ;
- n) $\text{-CONR}^{14}\text{R}^{14}$;
- o) $\text{-SO}_2\text{NR}^{14}\text{R}^{14}$;
- p) $\text{-SO}_2\text{R}^{13}$;
- 20 q) NO_2 ;
- r) $\overset{\text{O}}{\parallel} \text{-O-C-R}^{15}$;
- s) $\overset{\text{O}}{\parallel} \text{-O-C-NR}^{14}\text{R}^{14}$;
- 25 t) $\overset{\text{O}}{\parallel} \text{-O-C-OR}^{16}$;
- u) CN ;
- v) N_3 ;

R^7 is H or alkyl of 1 to 6 carbons;

30 R^8 is H or alkyl of 1 to 6 carbon atoms;

each R^9 is independently H, OH, C_1 to

C_4 -O-alkyl or alkyl of 1 to 4 carbons;

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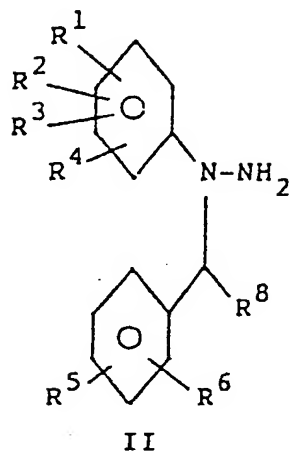
- R^{10} is COOH; CH_2OH ; CHO; tetrazole;
 $NHSO_2R^{11}$ wherein R^{11} is OH, alkyl or alkoxy of
 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,
 phenyl or phenyl substituted by alkyl or alkoxy
 5 groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN,
 formyl or acyl to 1 to 6 carbons; $CONHSO_2R^{11}$;
 hydroxymethylketone; CN; or $CON(R^9)_2$;
 r is 1 to 6;
 each R^{13} independently is H; C_1 to C_6
 10 alkyl; benzyl; phenyl or substituted phenyl wherein
 the substituents are C_1 to C_3 alkyl, halogen, CN,
 CF_3 , $COOR^{14}$, CH_2COOR^{14} , C_1 to C_3 alkoxy,
 or C_1 to C_4 perfluoroalkyl;
 each R^{14} is independently H, phenyl,
 15 benzyl or C_1 to C_6 alkyl; and,
 each R^{15} independently is H,
 $(CH_2)_mCOOR^{14}$ wherein m is 0 to 4, C_1 to C_6
 alkyl, CF_3 , phenyl, or substituted phenyl wherein
 substituted phenyl is as defined above in the
 20 definition of R^{13} ;
 or a pharmaceutically acceptable salt thereof;
 which process comprises
 a) reacting a compound of formula II with a compound
 of formula III:

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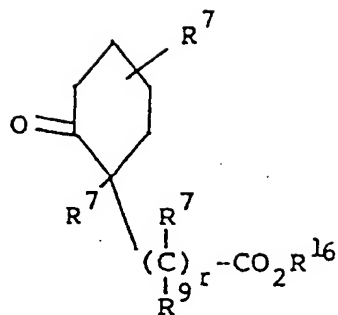
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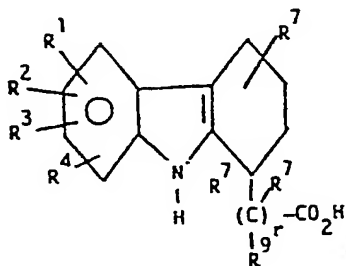


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wherein R^{16} represents an ester radical; to produce
 a compound of formula I wherein R^{10} represents COOH
 or an ester thereof; or
 b) reacting a compound of formula

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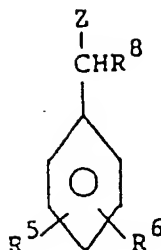


with a compound of formula (V):

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(V)

where Z is a leaving group; to produce a compound of formula I wherein R¹⁰ represents COOH or an ester thereof; and

- 5 c) after step (a) or step (b), optionally converting one group R¹⁰ to a different group R¹⁰.

2. A process as claimed in claim 1 for the preparation of a compound which is:

- 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
 17 3-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl]-propanoic acid;
 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl]-propanoic acid;
 15 9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
 2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl]-1 ethanol;
 3-[9-p-chlorobenzyl-6-methoxy-1,2,3,4-tetrahydrocarbazol-1-yl]-propanol;
 20

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- (-)9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
(+)9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
5 9-benzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-
acetic acid;
9-p-methoxybenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-
1-yl-acetic acid;
9-(3,4-dichloro)benzyl-6-fluoro-1,2,3,4-tetrahydro-
10 carbazol-1-yl-acetic acid;
9-[1-(1-phenyl)ethyl]-6-fluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic
acid;
15 9-p-chlorobenzyl-6-chloro-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;
9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;
6-bromo-9-p-chlorobenzyl-1,2,3,4-tetrahydrocarbazol-1-
20 yl-acetic acid;
9-p-chlorobenzyl-6-methyl-1,2,3,4-tetrahydrocarbazol-1-
yl acetic acid;
2-[9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol
-1-yl]-propanoic acid;
25 9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbozol-
1-yl-acetic acid;
3-[(α and β)-t-butyl-6-fluoro-9-(p-chlorobenzyl)-
1,2,3,4-tetrahydrocarbazol-1-yl]acetic acid;
9-p-chlorobenzyl-5-fluoro-1,2,3,4-tetrahydrocarbazol-1-
30 yl-acetic acid;
9-p-chlorobenzyl-7-fluoro-1,2,3,4-tetrahydrocarbazol-1-
yl-acetic acid;

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- 9-p-chlorobenzyl-5,7-dichloro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6,8-dichloro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid.
- 5 9-p-chlorobenzyl-6-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-tert-butyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-trifluoromethyl-1,2,3,4-tetra-
10 hydrocarbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methylthio-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 15 9-p-chlorobenzyl-6-methylsulfonyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-isopropyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-methylthio-1,2,3,4-tetrahydrocar-
20 bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-8-methylsulfinyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-fluoro-3-methyl-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 25 9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6,8-dimethyl-1,2,3,4-tetrahydrocar-
bazol-1-yl-acetic acid;
- 9-p-chlorobenzyl-6-methoxy-8-methyl-1,2,3,4-tetrahydro-
30 carbazol-1-yl-acetic acid;
- (-)-9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydro-
carbazol-1-yl-acetic acid;

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- (+)-9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(-)-9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
5 (+)-9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(-)-9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
(+)-9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
10 2-(9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl)ethanol;
(-) or (+) 2-(9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl)ethanol.

15

3. A process as claimed in claim 1 for the preparation of a compound which is:

- 9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
20 9-p-chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
9-p-chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
9-p-chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.
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4. A process as claimed in claim 1 for the preparation of a compound which is:

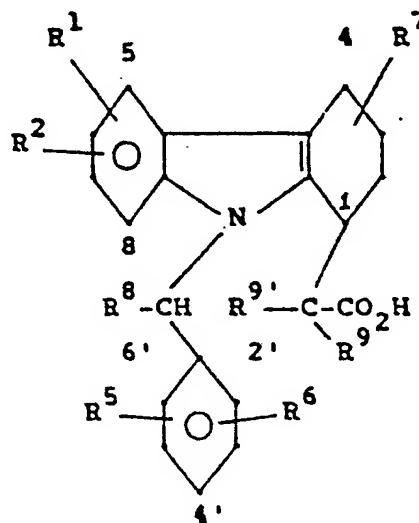
(-)-9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;

5 (-)-9-p-Chlorobenzyl-6,8-difluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;

(-)-9-p-Chlorobenzyl-8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;

10 (-)-9-p-Chlorobenzyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

5. A process as claimed in claim 1 for the preparation of a compound of the formula:



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wherein:

Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
5 1 (Ex. 1)	6-F	H	4'-Cl	H	H, H	H	H
2 (Ex. 4)	6-OMe	H	4'-Cl	H	H, H	H	H
10 3 (Ex. 7)	6-F	H	4'-Cl	H	H, H	H	H
	(-) isomer						
4 (Ex. 8)	6-F	H	4'-Cl	H	H, H	H	H
	(+) isomer						
15 5 (Ex. 9)	6-F	H	H	H	H, H	H	H
6 (Ex. 10)	6-F	H	4'-OMe	H	H, H	H	H
20 7 (Ex. 11)	6-F	H	3'-Cl	4'-Cl	H, H	H	H
8 (Ex. 12)	6-F	H	H	H	H, H	H	Me
9 (Ex. 13)	H	H	4'-Cl	H	H, H	H	H
25 10 (Ex. 14)	6-Cl	H	4'-Cl	H	H, H	H	H
11 (Ex. 15)	8-Me	H	4'-Cl	H	H, H	H	H
30 12 (Ex. 16)	6-Br	H	4'-Cl	H	H, H	H	H
13 (Ex. 17)	6-Me	H	4'-Cl	H	H, H	H	H

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Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
14 (Ex. 19)	8-F	H	4'-Cl	H	H, H	H	H
5 15 (Ex. 20)	6-F	H	4'-Cl	H	H, H	3-t-Bu	H
16 (Ex. 21)	5-F	H	4'-Cl	H	H, H	H	H
17 (Ex. 21)	7-F	H	4'-Cl	H	H, H	H	H
10 18 (Ex. 22)	5-Cl	7-Cl	4'-Cl	H	H, H	H	H
19 (Ex. 23)	6-Cl	8-Cl	4'-Cl	H	H, H	H	H
15 20 (Ex. 18)	6-F	H	4'-Cl	H	Me, H	H	H
21	6-F	H	4'-Cl	H	Me, Me	H	H
22	6-F	H	4'-Cl	H	H, H	1-Me	H
20 23	8-Br	H	4'-Cl	H	H, H	H	H
24 (Ex. 24)	6-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
25 25 (Ex. 25)	6-C(Me) ₃	H	4'-Cl	H	H, H	H	H
26 (Ex. 26)	6-CF ₃	H	4'-Cl	H	H, H	H	H
27 (Ex. 27)	6-SMe	H	4'-Cl	H	H, H	H	H
30 28 (Ex. 28)	6-S(O)Me	H	4'-Cl	H	H, H	H	H
29 (Ex. 29)	6-S(O) ₂ Me	H	4'-Cl	H	H, H	H	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	30 (Ex. 30)	8-CH(Me) ₂	H	4'-Cl	H	H, H	H	H
5	31 (Ex. 31)	8-SMe	H	4'-Cl	H	H, H	H	H
	32 (Ex. 32)	8-S(0)Me	H	4'-Cl	H	H, H	H	H
10	33 (Ex. 33)	6-F	H	4'-Cl	H	H, H	3-Me	H
	34 (Ex. 34)	6-F	8-F	4'-Cl	H	H, H	H	H
	35 (Ex. 35)	6-Me	8-Me	4'-Cl	H	H, H	H	H
15	36 (Ex. 36)	6-OMe	8-Me	4'-Cl	H	H, H	H	H
	37 (Ex. 37)	6-F(-) Isomer	8-F	4'-Cl	H	H, H	H	H
	38 (Ex. 38)	6-F(+) Isomer	8-F	4'-Cl	H	H, H	H	H
20	39 (Ex. 39)	8-Me(-) Isomer	H	4'-Cl	H	H, H	H	H
	40 (Ex. 40)	8-Me(+) Isomer	H	4'-Cl	H	H, H	H	H
25	41 (Ex. 41)	8-F(-) Isomer	H	4'-Cl	H	H, H	H	H
	42 (Ex. 42)	8-F(+) Isomer	H	4'-Cl	H	H, H	H	H
	43	6-F	8-F	3'-Cl	4'-Cl	H, H	H	H
30	44	6-F	8-F	2'-Cl	4'-Cl	H, H	H	H

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	Compound	R ¹	R ²	R ⁵	R ⁶	R ⁹ , R ^{9'}	R ⁷	R ⁸
	45	6-F	8-F	4'-OMe	H	H, H	H	H
5	46	6-F	8-F	4'-OH	H	H, H	H	H
	47	6-F	8-F	4'-SMe	H	H, H	H	H
	48	6-F	H	4'-S(O)Me	H	H, H	H	H
10	49	6-F	8-F	4'-NHCOMe	H	H, H	H	H
	50	6-F	H	4'-S(O) ₂ Me	H	H, H	H	H
15	51	6-F	H	4'-F	H	H, H	H	H
	52	6-F	H	4'-Br	H	H, H	H	H
	53	6-F	8-Me	4'-Cl	H	H, H	H	H
20	54	6-F	H	4'-CO ₂ H	H	H, H	H	H
	55	6-F	H	4'-CO ₂ Me	H	H, H	H	H
25	56	6-F	8-F	4'-n-C ₃ H ₇	H	H, H	H	H
	57	6-F	8-F	3'-I	4'-OH	H, H	H	H
	58	6-F	8-F	4'-I	H	H, H	H	H
30	59	6-N ₃	H	4'-Cl	H	H, H	H	H
	60	6-F	H	4'-N ₃	H	H, H	H	H

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6. A process for preparing a pharmaceutical composition which comprises mixing a compound of Formula I with a pharmaceutically acceptable carrier.

5 7. A process for preparing a pharmaceutical composition which comprises mixing a compound of Formula I with an effective amount of a second active ingredient selected from the group consisting of non-steroidal anti-inflammatory drugs; peripheral analgesic agents; cyclooxygenase
10 inhibitors; leukotriene antagonists; leukotriene biosynthesis inhibitors; H₁-receptor antagonists; H₂ receptor antagonists; prostaglandin antagonists; ACE inhibitors, or thromboxane synthetase inhibitors.

15 8. A process as claimed in claim 7 wherein the second active ingredient is a non-steroidal anti-inflammatory drug.

9. A process as claimed in claim 8 wherein the non-steroidal anti-inflammatory drug is
20 indomethacin.

10. A process as claimed in claim 7 wherein the weight ratio of said compound of Formula I to said second active ingredient ranges from about 200:1 to 1:200.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application number
0234708

EP 87 30 0449

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D,A	US-A-4 057 559 (ASSELIN et al.) * Whole document *	1-10	C 07 D 209/86 C 07 D 209/88 A 61 K 31/40

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A	FR-A-2 103 403 (N.V. ORGANON) * Whole document *	1-10	

P,X	EP-A-0 200 391 (AMERICAN HOME PRODUCTS CORP.) * Columns 3-6 *	1-10	

			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 209/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11-03-1987	Examiner MAISONNEUVE, J.A.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	